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A COMPARATIVE EVALUATION OF SULFONAMIDES

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THE place of sulfonamide compounds in the management of infectious diseases is of importance to the pediatrician for a number of reasons. In the past decade many new sulfonamides have been introduced which appear to have certain advantages over earlier preparations. Successful modifications of the sulfanilamide molecule designed to increase therapeutic effectiveness or to lessen the incidence of complications have been achieved. As selective inhibition increases the number of microorganisms resistant to the available antibiotics, new therapeutic problems are presented to the clinician. In some instances the management of infections due to resistant microorganisms may be improved through the use of sulfonamides, either alone or in combinations with an antibiotic agent. It seems probable that the more frequent use of sulfonamides for common clinical conditions may decrease the incidence of disease due to antibiotic resistant microorganisms. Serious toxicity and other complications of chemotherapy with the newer sulfonamides are strikingly low. Several microorganisms are as effectively inhibited by sulfonamides as by the antibiotics, for example, meningococci, pneumococci, and shigella. Finally the much lower cost to the patient of sulfonamide therapy, is an item to be considered.

These considerations have encouraged us to re-evaluate the present status of sulfonamide therapy from two points of view. The first section of this report is devoted to a review and discussion of the newer sulfonamide preparations and their therapeutic efficacy. The second portion presents an experimental comparison of the level of free sulfonamide found in the body fluids after single and multiple dose administration of the more commonly used preparations, and some of the newer sulfonamides.

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PART I: THERAPY WITH SULFONAMIDES

The chemotherapeutic use of sulfonamide compounds originated with the discovery by Domagk, Klarer, and

Mietisch in 1932 of the therapeutic effectiveness of Prontosil.[1] Three years later, in 1935, Levaditi and Vaisman[2] recognized that the therapeutically effective moiety of Prontosil was the para-aminobenzene sulfonamide group. This group was synthesized by Fourneau[3] and given the name sulfanilamide. He also demonstrated the chemotherapeutic effectiveness of sulfanilamide against streptococci and this finding was confirmed by others. In 1937 Ewins and Phillips introduced a modification of the sulfanilamide molecule, were altered, antimicrobial potency diminished.

Following sulfapyridine came sulfathiazole which was effective against the pneumococcus, gonococcus, streptococcus, meningococcus, and shigella. In addition, sulfathiazole was less toxic than either sulfanilamide or sulfapyridine. With the introduction in 1941 of sulfadiazine,[4] sulfonamide therapy reached a peak of popularity. Sulfadiazine though relatively slowly absorbed was also slowly excreted and so gave sustained blood levels (Fig. 1).

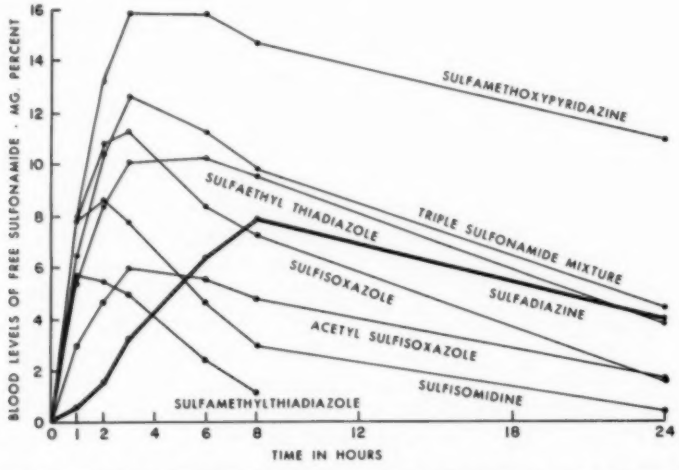

Fig. 1.—Mean blood free sulfonamide levels obtained following the oral administration of a single dose of 100 mg. per kilogram of body weight for eight sulfonamide preparations.

sulfapyridine, which was found to be particularly effective against the pneumococcus. In the next decade modifications of the sulfanilamide molecule were numerous. Early experience indicated that if the antimicrobial activity of sulfanilamide was to be preserved, modifications of its structure must be limited to substitutions for the hydrogen ions of the sulfonamide portion. When other portions of the basic sulfanilamide structure In addition, toxic reactions associated with its use, such as agranulocytosis, skin rash, and hematuria, were much less common. Its antimicrobial spectrum embraced the majority of the gram-negative bacilli, and in addition, the streptococcus, pneumococcus, meningococcus, and gonococcus. Widespread clinical use has amply supported the early claims of its efficacy.

Sulfamerazine, the monomethyl derivative of sulfadiazine, was introduced

by Roblin and associates[5] in 1940 and has similar antibacterial activity. This sulfonamide is more rapidly and completely absorbed than sulfadiazine, but has enjoyed less general popularity because of a higher incidence of undesirable side effects when used alone.

The dimethylated derivative of sulfadiazine, sulfamethazine, was introduced by Sprague and co-workers[6] in 1941 and shows even more rapid absorption and excretion than sulfamerazine. It has been used principally as a component of mixtures along with sulfadiazine and sulfamerazine.

The same years that saw the introduction of sulfadiazine also gave physicians the first glimpse of the antibiotics, for in 1942 Fleming described the clinical effectiveness of penicillin against a wide variety of microorganisms. Penicillin and the other antibiotic preparations that followed were dramatically effective and appeared to be remarkably free from toxic reactions even when given in massive doses. It is therefore not surprising that physicians, weary of regulating blood levels, alkalinizing the urine, and ensuring a large fluid intake during sulfonamide therapy, should substitute antibiotic agents for sulfonamide preparations. The problems of agranulocytosis, aplastic anemia, methemoglobinemia, hemolytic anemia, jaundice, dermatitis, drug fever, and the fear of production of disturbances in collagen seemed to be things of the past. The introduction of penicillin was rapidly followed by the announcement of other antibiotic agents that covered the spectrum of all the pathogenic bacteria, spirochetes, and rickettsiales (which include all the rickettsiae and some of the larger viruses). For a time it appeared that antibiotic therapy would completely supplant the need for chemotherapeutic agents. However, problems of antibiotic therapy soon began to appear: sensitivity reactions to penicillin, acoustic nerve damage by streptomycin, and the rapid emergence of resistant microorganisms during therapy. Therapy with the tetracyclines and chloramphenicol was often associated with gastroenteritis and marked alteration in normal gastrointestinal flora, sometimes with the substitution of infections due to monilia or resistant microorganisms.

At the end of the first decade of antibiotic therapy problems associated with their use are now fairly well defined. The incidence of allergic reactions to penicillin approaches 10 per cent and over forty fatal anaphylactic reactions have been reported.[7] Forty-four deaths due to aplastic anemia in association with antibiotic therapy, principally chloramphenicol and streptomycin, have been reported.[8] Many observers are concerned over the rising incidence of infections due to antibiotic-resistant microorganisms, not to mention the problems of superinfection in the course of antibiotic therapy.

That these problems are being more generally appreciated is shown by the fact that in 1954, on an individual dose basis, sulfonamide preparations were second only to penicillin according to the data of the Food and Drug Administration. The increasing trend to the use of sulfonamide preparations suggests a desire on the part of physicians to reserve antibiotic preparations for specific use or where rapid control of the infection is necessary.

During the "antibiotic era," enthusiasm for the rapid and often dramatic-acting antibiotic agents has tended to

overshadow developments in the chemotherapy of infections. While a host of new antibiotics were being developed other research workers continued to seek new sulfonamides or to eliminate the undesirable side effects of known sulfonamide preparations.

Lehr,[8] in 1940, introduced the concept of combinations of sulfonamides. The solubility of each drug in the body fluids is independent of the others present while their antibacterial activity is additive. This meant that a mixture of two or three different sulfonamides was two to three times more soluble while equally as effective as a similar quantity of a single sulfonamide. In addition, it was felt that allergic or hypersensitivity reactions to sulfonamides were significantly less when individual blood levels were kept below 5 mg. per cent. Therapy with triple sulfonamide mixture created effective blood levels while concentrations of the individual drug remained below this level. By combining sulfonamides of different absorption, distribution, and excretion patterns, rapid absorption and prolonged levels could be achieved (Fig. 1). Such preparations virtually eliminated the problem of the renal toxicity of sulfonamides due to crystal formation and renal tubular obstruction. In this country a widely used combination is that of equal quantities of sulfadiazine, sulfamerazine, and sulfamethazine in either tablets or oral suspension (Tables IV and XII).

In 1946 the appearance of sulfisoxazole* marked the entry into clinical medicine of the highly soluble sulfonamides.[9] Sulfisoxazole is well absorbed (Tables II and X) and possesses the advantages of marked solubility (solubility at pH 6 approximately ten times that of sulfadiazine) in the normal pH range of urine, thus eliminating the need for alkali administration and the maintenance of a high fluid intake. It was shown to be as effective a chemotherapeutic agent as sulfadiazine, yet singularly free of undesirable side effects.

Taste of a sulfonamide is related to its solubility and the highly soluble sulfisoxazole proved to be exceeding bitter, thus making it difficult to administer to children. In an effort to overcome this defect the less soluble derivative, acetylsulfisoxazole, was studied.[10] It proved to have an easily disguised taste and was split by intestinal bacteria to the highly soluble nonacetylated form, sulfisoxazole, which is readily absorbed and appeared in the blood of patients treated with acetylsulfisoxazole. However, the reduced solubility of the acetyl form led to lower blood levels of free sulfonamide following a given dose (Fig. 1). The earlier observations concerning lipid vehicles for sulfonamides were therefore investigated in an effort to improve absorption of acetylsulfisoxazole.

The recent trend to the administration of sulfonamide preparations in a lipid emulsion vehicle stems from the observations of Finestone and associates[11] in 1940 and of Peterson and Finland[12] in 1942. They noted that fat emulsions tended to improve both the rate and degree of absorption of a sulfonamide and that sulfonamides given with a meal showed improved absorption. The recently available preparations of acetylsulfisoxazole, sulfadiazine, and triple sulfonamides in

*The trade name of Hoffmann-La Roche for sulfisoxazole is Gantrisin.

stable fat emulsion utilize these observations. The prolonged levels obtained by these preparations (Fig. 2) has led to the recommendation of a dosage interval of 8 to 12 hours as opposed to the usual dose frequency of every 6 hours. The efficacy of this principle of sulfonamide administration has been confirmed by others[13-15] and appears to represent a significant improvement in sulfonamide dosage form for children.

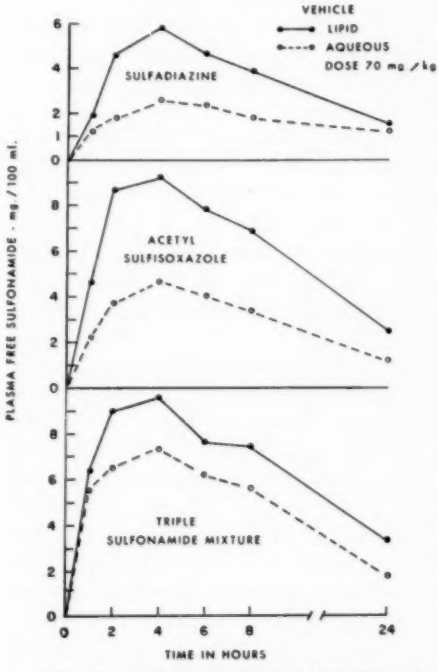

Fig. 2.—The comparative absorption of three commonly used sulfonamide preparations from a standard aqueous suspension and from a lipoemulsion. The improved absorption in the lipoemulsions is found consistently. (From Terrell, W., Yow, E. M., and Daeschner, C. W.: M. Clin. North America, March 1957.)

Although sulfaethylthiadiazole was prepared in 1940,[16] interest in this country in its chemotherapeutic value did not develop until recently. This compound represents a moderately soluble sulfonamide. It is rapidly and almost completely absorbed, and due to a fairly high rate of tubular reabsorption (i.e., low renal clearance rate), blood levels are sustained (Table V). Its degree of acetylation is less than that of other sulfonamides with the exception of sulfamethylthiadiazole. Clinical experience in this country with sulfaethylthiadiazole is limited, but reports in the European literature suggest that its chemotherapeutic range is similar to that of sulfadiazine.

Sulfamethylthiadiazole* (Table VI) was introduced orginally in 1944[17] but not marketed in this country until 1951. It is rapidly absorbed, sparingly acetylated, and excreted rapidly in the urine, where it is moderately soluble at usual urinary pH range.

Sulfisomidine (sulfadimidine)† (Table VII), as isomer of sulfamethazine, is rapidly absorbed and excreted in a manner quite similar to sulfamethylthiadiazole.[18] Acetylation is low and urinary levels of free sulfonamide are high. It diffuses readily into cerebrospinal, ascitic, and pleural fluid. Its principal use has been in the treatment of lower urinary tract infections.

Sulfamethoxypyridazine‡ (Table VIII) was developed in this country and is in the phase of initial clinical trials.[19] Due to the very low renal clearance rates of this sulfonamide (high degree of tubular reabsorption), effective blood levels persist for forty-

*The trade name of Ayerst Laboratories, Inc., for sulfamethylthiadiazole is Thiosulfil.

†The trade name of Ciba Pharmaceutical Products, Inc., for sulfisomidine is Elkosin.

‡The trade name of American Cyanamid Co. (Lederle Laboratories Division) for sulfamethoxypyridazine is Kynex.

eight to ninety-six hours after a single oral dose. It is rapidly absorbed from the gastrointestinal tract, highly soluble in urine, and shows only a moderate degree of acetylation. It is thought to possess antibacterial activity similar to that of sulfadiazine.

PART II: EXPERIMENTAL STUDIES

The following studies were undertaken to compare the blood sulfonamide levels obtained following the oral administration of sulfadiazine, sulfisoxazole, acetylsulfisoxazole, a triple sulfonamide mixture, sulfaethylthiadiazole, sulfamethylthiadiazole, sulfadimidine, and sulfamethoxypyridazine. In addition, studies have been carried out to determine the cerebrospinal fluid concentration of several of these sulfonamides in relation to their blood level.

Materials and Methods.—The sulfadiazine suspension used contained 500 mg. per 5 ml. in an orange-flavored aqueous suspension. Sulfisoxazole in aqueous suspension contained 500 mg. per 5 ml. in a strawberry-flavored vehicle. Triple sulfonamide mixtures contained 167 mg. sulfadiazine, 167 mg. sulfamerazine, and 167 mg. sulfamethazine per 5 ml. in a chocolate-flavored aqueous suspension. Acetylsulfisoxazole was supplied in a vanilla-flavored aqueous suspension containing 593 mg. per 5 ml. This concentration was calculated as the molecular equivalent of 500 mg. of sulfisoxazole. Hereafter, in all stated doses 500 mg. of acetylsulfisoxazole is actually 593 mg. of the drug. Sulfaethylthiadiazole was supplied as a prolonged action suspension containing 650 mg. per ml. in a strawberry-flavored vehicle. Sulfamethylthiadiazole was administered as a vanilla-flavored aqueous suspension containing 250 mg. per 5 ml. The sulfamethoxypyridazine was available in tablets of 0.5 Gm. each; these were crushed and given in water. The sulfadimidine preparation given contained 500 mg. per 5 ml. in an aqueous strawberry-flavored suspension.

Hospitalized children from ages 1 month to 13 years were selected for this study. The children were hospitalized for the usual illnesses seen on a general pediatric service.

After drawing a control blood specimen, *single oral doses* of 100 mg. per kilogram of the sulfonamide to be studied was given. The number of children in each group are shown on the individual tables. Blood specimens were obtained at 1, 2, 3, 6, 8, and 24 hours and the free blood sulfonamide level determined.

A multiple dose schedule was studied for sulfadiazine, sulfisoxazole, and acetylsulfisoxazole, a triple sulfonamide mixture, and sulfaethylthiadiazole. The interval utilized was based upon the levels obtained in the single dose studies. These children were given 100 mg. per kilogram initially, and 50 mg. per kilogram every 6 hours for 72 hours except in the sulfaethylthiadiazole studies where an interval of every 12 hours was utilized. Blood specimens for free sulfonamide concentration were obtained prior to administration of the drug and at intervals as indicated in the tables.

In fifty children the cerebrospinal fluid concentration of free sulfonamide was determined. Blood levels were determined at the same time.

The Bratton-Marshall capillary method of determining the free blood sulfonamide level was followed, using the photoelectric colorimetric method

TABLE I. BLOOD LEVELS OF FREE SULFONAMIDE FOLLOWING SINGLE ORAL DOSE OF SULFADIAZINE OF 100 MG. PER KILOGRAM OF BODY WEIGHT

NAME	WT. (KG.)	HOURS AFTER ADMINISTRATION					
		1	2	3	6	8	24
D. W.	2.5	0.0	0.5	2.3	3.4	3.4	1.2
F. F.	4.5	0.9	2.4	3.8	5.3	5.2	2.1
M. B.	5.0	0.0	0.2	0.3	4.9	10.1	6.0
J. B.	9.0	1.8	3.4	5.0	7.2	7.3	4.2
P. T.	9.0	2.4	5.1	9.5	12.8	14.4	6.0
R. L. H.	19.0	0.0	0.0	0.0	4.7	10.5	4.5
C. H.	24.0	0.0	0.3	0.3	1.2	2.4	4.5
P. M.	26.0	0.0	0.5	4.3	8.1	8.1	4.3
L. H.	47.0	0.3	1.7	4.5	9.8	9.8	3.6
Mean (9)		0.6	1.6	3.3	6.4	7.9	4.0
Range: Lowest		0.0	0.0	0.0	1.2	2.4	1.2
Highest		2.4	5.1	9.5	12.8	14.4	6.0

TABLE II. BLOOD LEVELS OF FREE SULFONAMIDE FOLLOWING SINGLE ORAL DOSE OF ACETYLSULFISOXAZOLE OF 100 MG. PER KILOGRAM OF BODY WEIGHT

NAME	WT. (KG.)	HOURS AFTER ADMINISTRATION					
		1	2	3	6	8	24
B. J.	2.0	1.8	4.8	4.8	6.1	6.9	1.2
D. W.	2.5	6.1	8.4	12.2	17.7	24.3	8.7
D. W.	2.5	2.5	3.3	4.1	12.5	11.1	1.7
D. W.	2.5	0.6	4.5	11.1	8.9	6.8	1.3
G. D.	3.0	7.9	12.6	18.5	15.5	12.6	8.9
C. D.	4.0	4.1	4.3	5.6	10.2	9.3	0.7
D. M.	4.0	10.2	16.2	15.6	11.6	9.3	2.5
C. B.	4.0	13.9	12.9	12.7	6.9	5.3	0.8
F. F.	4.5	8.7	11.2	9.6	7.8	5.8	0.8
R. P.	5.0	11.9	14.2	13.4	12.9	9.4	0.8
M. B.	5.0	3.5	4.3	8.9	9.2	8.3	2.1
R. P.	5.0	2.5	6.1	9.0	7.5	6.1	0.4
J. A.	7.0	16.0	15.0	14.8	4.3	3.3	0.0
P. C.	7.5	8.1	11.2	10.4	3.9	3.1	0.0
P. C.	8.0	7.2	14.1	16.5	8.4	5.1	0.5
J. C.	9.0	7.7	14.9	16.7	10.5	9.2	1.0
P. T.	9.0	3.9	10.9	13.0	9.5	7.2	1.5
J. C.	9.0	2.5	3.4	4.1	6.4	5.1	0.9
J. B.	9.0	3.0	10.7	11.6	6.5	6.0	0.5
C. C.	11.0	11.5	11.5	7.0	5.1	0.8	0.0
C. C.	11.0	3.1	6.1	9.3	7.1	5.5	0.6
R. J.	12.5	10.2	17.4	19.0	9.0	5.0	0.3
V. K.	12.5	11.1	19.2	12.3	5.8	3.6	0.3
S. W.	17.0	12.7	16.2	11.6	8.4	6.9	1.7
P. K.	19.0	9.9	11.2	12.0	7.8	8.1	--
C. H.	19.0	6.6	16.5	16.5	12.7	9.9	1.0
R. L. H.	19.0	14.4	13.2	10.9	6.6	4.8	1.1
J. W.	19.0	8.4	11.2	9.9	4.6	4.4	1.0
C. H.	24.0	3.6	4.8	6.8	7.2	5.8	1.3
P. M.	25.0	17.6	17.6	12.8	4.9	4.2	0.1
T. S.	40.0	1.4	8.5	8.4	7.3	12.0	6.1
L. H.	46.0	18.1	13.9	10.9	7.5	5.4	0.4
Mean (32)		7.8	10.9	11.3	8.4	7.2	1.6
Range: Lowest		0.6	3.3	4.1	3.9	0.8	0.0
Highest		18.1	19.2	19.0	17.7	24.3	8.9

as outlined in Hepler's *Manual of Clinical Laboratory Methods.* Standard curves for each preparation used were obtained periodically throughout the study and the mean standard curve of each was used to determine the final concentration of the individual sulfonamide.

RESULTS

The individual and mean values for free sulfonamide in the blood following a single oral dose of 100 mg. per kilogram of body weight are shown in Tables I to VIII. Fig. 1 is a graphic illustration of the mean values.

Single Dose Studies.—Nine children were given a single oral dose of sulfadiazine (Table I), following which the blood sulfonamide level reached a maximum by 6 hours in three patients and by 8 hours in the remaining six patients. The lowest peak blood level was 3.4 mg. per cent and occurred in one child. The blood sulfonamide level in two children reached a peak of less than 6.0 mg. per cent, while the remaining five subjects had levels greater than 7.0 mg. per cent (7.3 to 14.4 mg. per cent).

Thirty-two children were given sulfisoxazole in a single oral dose (Table II). The lowest peak blood sulfonamide level was 6.9 mg. per cent (at 8 hours in a 2.0 kilogram infant), while only three children had blood levels less than 10.0 mg. per cent.

In twenty-six children who received a single oral dose of acetylsulfisoxazole (Table III) the maximum blood level was less than 6.0 mg. per cent in ten,

TABLE III. BLOOD LEVELS OF FREE SULFONAMIDE FOLLOWING SINGLE ORAL DOSE OF ACETYLSULFISOXAZOLE OF 100 MG. PER KILOGRAM OF BODY WEIGHT

NAME	WT. (KG.)	HOURS AFTER ADMINISTRATION					
		1	2	3	6	8	24
B. J.	2.0	0.4	0.9	1.8	4.1	5.1	1.8
D. W.	2.5	1.7	2.1	2.8	3.3	3.0	3.0
D. W.	2.5	2.2	2.6	5.0	6.8	6.3	1.7
D. W.	2.5	4.1	5.1	7.0	5.1	4.6	1.8
G. D.	3.0	2.0	4.0	4.7	4.5	4.7	1.2
C. B.	3.5	1.3	2.5	3.9	--	3.7	0.1
C. B.	4.0	6.9	7.2	7.2	5.1	3.8	1.0
C. B.	4.0	0.6	1.2	1.6	2.0	1.6	--
F. F.	4.5	2.1	2.1	2.3	2.5	2.7	0.7
M. B.	5.0	0.8	2.7	4.5	7.1	6.2	4.3
R. P.	5.0	2.8	7.9	11.5	8.0	6.8	1.6
P. C.	7.5	5.0	6.8	5.4	4.0	2.7	0.6
P. C.	8.0	1.9	3.2	2.8	1.3	1.1	0.1
J. B.	9.0	5.5	6.5	7.1	3.9	3.2	1.1
P. T.	9.0	3.2	4.6	9.9	10.2	7.2	2.5
J. C.	9.0	2.2	4.7	5.5	8.9	8.9	2.3
C. C.	11.0	2.7	3.3	5.8	5.1	4.7	2.0
R. J.	12.5	2.9	7.3	12.9	14.1	8.9	0.6
V. K.	12.5	3.6	9.0	7.2	5.3	4.4	1.9
D. P.	18.0	3.1	--	7.1	8.7	--	4.2
J. W.	19.0	7.1	7.4	6.8	6.0	6.5	1.6
C. H.	19.0	1.4	5.6	8.1	5.5	4.6	0.8
R. L. H.	19.0	6.1	10.1	12.3	6.6	5.6	0.9
C. H.	24.0	0.8	0.9	1.1	3.0	3.6	2.3
P. M.	25.0	1.8	4.1	5.1	3.6	3.6	1.4
L. H.	46.0	4.7	5.3	5.8	6.3	5.3	1.1
Mean (26)		3.0	4.7	6.0	5.6	4.8	1.7
Range: Lowest		0.4	0.9	1.1	1.3	1.1	0.1
Highest		7.1	10.1	12.9	14.1	8.9	4.3

less than 5.0 mg. per cent in seven, and less than 4.0 mg. per cent in six. The highest individual blood sulfonamide level achieved in this group was 14.1 mg. per cent, and only four children had blood levels over 10.0 mg. per cent. cent, while two children had maximum blood levels less than 10 mg. per cent.

Sulfaethylthiadiazole (Table V) was administered to six children in a dose of 100 mg. per kilogram. A peak level was reached by all patients by the third

TABLE IV. BLOOD LEVELS OF FREE SULFONAMIDE FOLLOWING SINGLE ORAL DOSE OF A TRIPLE SULFONAMIDE MIXTURE 100 MG. PER KILOGRAM OF BODY WEIGHT

NAME	WT. (KG.)	HOURS AFTER ADMINISTRATION					
		1	2	3	6	8	24
D. W.	2.5	1.2	3.0	10.2	10.2	9.6	3.9
M. B.	5.0	4.5	8.7	8.1	8.9	6.9	1.8
J. B.	9.0	0.8	4.7	8.5	7.3	6.8	6.3
R. L. H.	19.0	10.7	12.5	14.5	10.2	7.9	2.9
C. H.	24.0	5.7	8.9	10.8	11.3	9.8	4.0
P. M.	26.0	9.5	15.5	16.1	13.7	13.1	5.5
L. H.	47.0	12.8	19.2	20.4	17.8	14.4	6.1
Mean (7)		6.5	10.4	12.7	11.3	9.8	4.4
Range: Lowest		0.8	3.0	8.1	7.3	6.8	1.8
Highest		12.8	19.2	20.4	17.8	14.4	6.3

TABLE V. BLOOD LEVELS OF FREE SULFONAMIDE FOLLOWING SINGLE ORAL DOSES OF SULFAETHYLTHIADIAZOLE IN SPANSULE SUSPENSION OF 100 MG. PER KILOGRAM OF BODY WEIGHT

NAME	WT. (KG.)	HOURS AFTER ADMINISTRATION					
		1	2	3	6	8	24
W. S.	11	4.1	6.8	11.2	8.7	7.3	4.1
J. W. P.	12	5.2	9.1	10.6	7.8	5.6	2.0
P. L.	20	6.0	9.3	9.9	9.1	7.4	2.8
S. J.	21	8.1	12.1	12.5	9.6	6.9	
M. J.	23	6.6	9.7	10.0	15.7	18.3	7.1
P. M.	38	2.1	3.8	6.7	11.1	12.4	3.6
Mean (6)		5.35	8.47	10.15	10.3	9.65	3.9
Range: Lowest		2.1	3.8	6.7	7.8	5.6	2.0
Highest		8.1	12.1	12.5	15.7	18.3	7.1

TABLE VI. BLOOD LEVELS OF FREE SULFONAMIDE FOLLOWING SINGLE ORAL DOSES OF SULFAMETHYLTHIADIAZOLE OF 100 MG. PER KILOGRAM OF BODY WEIGHT

NAME	WT. (KG.)	HOURS AFTER ADMINISTRATION					
		1	2	3	6	8	24
D. M.	13	6.5	6.4	4.3	1.4	0.7	0.4
A. H.	15	0.8	0.9	1.1	4.3	1.6	0.3
L. T.	18	4.5		6.7	1.4	0.2	0.0
J. T.	27	9.0	6.3	6.5	3.1	0.9	0.4
B. L.	38	6.0	7.8	4.5	3.0	2.7	0.2
C. E. B.	45	7.5	6.2	6.1	1.4	0.5	0.1
Mean (6)		5.7	5.52	4.97	2.43	1.1	0.23
Range: Lowest		0.8	0.9	1.1	1.4	0.2	0.0
Highest		9.0	7.8	6.7	4.3	2.7	0.4

Triple sulfonamide preparations were administered in a single oral dose to seven children (Table IV). The lowest peak blood sulfonamide level in this group was 8.5 mg. per hour. The highest peak level was 18.3 mg. per cent and the lowest peak was 9.9 mg. per cent. The 24-hour levels varied from 2 to 7.1 mg. per cent, with a mean of 3.9 mg. per cent.

Six patients received sulfamethylthiadiazole (Table VI) in a single oral dose of 100 mg. per kilogram. A peak level occurred in the first hour in three patients, and in the second, third, and sixth hours, respectively, in the remaining three patients. The levels fell rapidly and varied from 0.2 to 2.7 mg. per cent at 8 hours, while all subjects had levels below 0.5 mg. per cent by 24 hours.

Sulfisomidine (Table VII) was administered in 100 mg. per kilogram single doses to six children. Two showed peak levels in the first hour, two in the second, and the remaining two in the third hour. A tendency to very rapid absorption and excretion is reflected in the main values with a peak in the second hour and a fall to 35 per cent of the peak level by the eighth hour.

Sulfamethoxypyridazine (Table VIII) was administered in a dose of 100 mg. per kilogram to nine subjects. The drug was rapidly and completely absorbed with an average level of 8.0 mg. per cent within the first hour and a peak level of 15.9 mg. per cent at 3 hours. The average 24-hour level is 11.0 mg. per cent and significant levels are still present at 48 hours.

Multiple Dose Studies.—A multiple dose schedule of 100 mg. per kilogram initially and 50 mg. per kilogram at the intervals indicated was given to forty-nine infants and children. The individual blood sulfonamide levels obtained in this phase of the study are

TABLE VII. BLOOD LEVELS OF FREE SULFONAMIDE FOLLOWING SINGLE ORAL DOSES OF SULFISOMIDINE OF 100 MG. PER KILOGRAM OF BODY WEIGHT

NAME	WT. (KG.)	HOURS AFTER ADMINISTRATION					
		1	2	3	6	8	24
M. S.	10	10.7	10.5	7.3	4.1	1.9	0.1
D. B.	13	5.0	6.3	6.1	3.8	2.4	1.0
D. M.	15	11.6	10.0	8.0	4.4	2.7	0.3
W. L.	16	7.1	7.5	8.1	5.0	3.6	0.3
K. D.	26	5.1	9.9	8.3	5.7	4.0	0.7
G. R.	35	7.6	7.2	8.7	5.3	3.6	0.2
Mean (6)		7.95	8.6	7.8	4.7	3.0	0.4
Range: Lowest		5.0	6.3	6.1	3.8	1.9	0.1
Highest		11.6	10.5	8.7	5.7	4.0	1.0

TABLE VIII. BLOOD LEVELS OF FREE SULFONAMIDE FOLLOWING SINGLE ORAL DOSES OF SULFAMETHOXYPYRIDAZINE OF 100 MG. PER KILOGRAM OF BODY WEIGHT

NAME	AGE (YR.)	WT. (KG.)	HOURS AFTER ADMINISTRATION								
			1	2	3	6	8	24	27	30	48
D. E.	5	16	0.4	11.6	17.8	16.6	16.4	9.8	8.6	6.4	4.6
B. R.	5	18	8.6	15.5	17.6	16.7	16.7	13.5	14.5	13.7	8.5
J. D.	5	22	8.5	11.0	11.2	13.2	6.9	6.3			
E. T.	5	23	14.8	17.5	19.0	17.5	16.6	11.8	12.8	10.8	6.5
P. G.	6	30	13.4	13.8	16.2	14.4	13.6	5.7	4.4	4.2	
C. S.	6	24	9.0	15.5	15.5	14.0	13.7	10.0	8.8	8.6	4.9
M. T.	11	32	10.1	13.6	13.6	14.8	14.8	14.4	15.0	15.2	10.1
L. C.	13	25	4.8	10.0	13.4	17.4	18.0	13.2	14.2	12.6	
C. B.	13	47	2.0	10.2	15.6	18.3	15.9	14.3	15.3	14.1	10.1
Mean (9)			8.0	13.2	15.9	15.9	14.7	11.0	11.7	10.7	7.5
Range: Lowest			0.4	10.0	11.2	13.2	6.9	5.7	4.4	4.2	4.6
Highest			14.8	17.5	19.0	18.3	18.0	14.4	15.3	15.2	10.1

shown in Tables IX to XIII. The 1-, 2-, 3-, and 6-hour blood levels in these patients were similar to those shown in Tables I to V for the single oral dose studies. Fig. 3 illustrates the mean blood sulfonamide levels produced by these multiple dose schedules.

Six patients received sulfadiazine orally on a multiple dose schedule (Table IX). The individual blood levels varied from 2.6 to 14.1 mg. per cent and reached 7 mg. per cent in all six children. The average blood sulfonamide level after the first six hours was 5.8 mg. per cent and ranged from 4.6 to 7.5 mg. per cent.

Sulfisoxazole in multiple oral dose schedule was given to ten infants and children (Table X). The mean blood levels after six hours ranged from 4.6 to 6.8 mg. per cent and averaged 5.8 mg. per cent. The individual blood sulfonamide levels after the sixth hour ranged from 1.4 to 12.8 mg. per cent in all but one patient, a blood level greater than 7.0 mg. per cent was reached.

Continuous therapy in sixteen patients (Table XI) with acetylsulfisoxazole produced a mean blood level in the 24- to 76-hour interval of 4.1 to 6.0 mg. per cent with mean of 5.2 mg. per cent. The range of individual blood sulfonamide levels for this interval was 0.3 to 12.3 mg. per cent.

Triple sulfonamide mixtures were given in multiple oral dose to eleven children (Table XII). The mean blood level after the first six hours varied from 12.2 to 16.4 mg. per cent

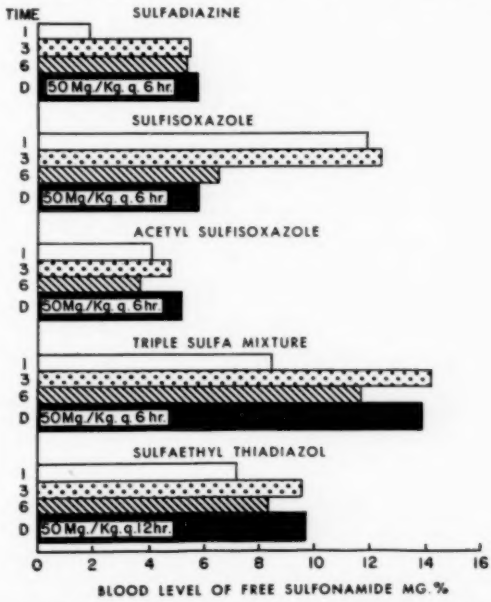

Fig. 3.—A summary of the multiple dose oral sulfonamide studies. The patients were given an initial dose of 100 mg. per kilogram of body weight followed by 50 mg. per kilogram every 6 to 12 hours as indicated on the chart. Mean blood sulfonamide levels following the drug are illustrated as follows: Clear column, level at 1 hour; dotted column, level at 3 hours; cross-hatched column, level at 6 hours. The solid column represents the average of all determinations from the sixth through the seventy-sixth hour of therapy.

TABLE IX. BLOOD LEVELS OF FREE SULFONAMIDE FOLLOWING MULTIPLE ORAL DOSES OF SULFADIAZINE
(100 mg. per Kilogram Initially and 50 mg. per Kilogram Every 6 Hours)

NAME	WT. (KG.)	HOURS AFTER INITIAL DOSE												
		1	2	3	6	24	26	28	48	50	52	72	74	76
B. M.	3.5	0.9	1.3	1.4	1.3	4.9	5.6	7.0	5.2	5.6	6.0	2.6	4.0	4.1
L. J.	20.0	3.2	7.2	7.2	5.4	6.6	8.2	8.0	11.9	14.1	13.1	9.6	11.1	11.2
R. L. H.	20.0	1.5	4.6	6.5	7.3	7.6	7.1	5.7	7.6	5.4	5.5	8.2	8.2	6.5
M. C.	31.0	1.7	4.3	5.3	4.4	7.0	9.1	7.3	--	--	--	--	--	--
H. L. W.	34.0	0.6	3.8	5.5	8.2	5.2	6.1	5.9	6.5	6.7	7.1	5.7	5.6	4.6
I. A.	35.0	3.2	5.9	7.0	5.9	5.6	5.0	5.1	4.3	4.9	5.7	4.2	3.4	2.7
Mean (6)		1.9	4.5	5.5	5.4	6.2	6.9	6.5	7.1	7.3	7.5	6.1	6.5	5.8
Range: Lowest		0.6	1.3	1.4	1.3	4.9	5.0	5.1	4.3	4.9	5.5	2.6	3.4	2.7
Highest		3.2	7.2	7.2	8.2	7.6	9.1	8.0	11.9	14.1	13.1	9.6	11.1	11.2

TABLE X. BLOOD LEVELS OF FREE SULFONAMIDE FOLLOWING ADMINISTRATION OF MULTIPLE ORAL DOSES OF SULFISOXAZOLE
(100 mg. per Kilogram Initially and 50 mg. per Kilogram Every 6 Hours)

NAME	WT. (KG.)	HOURS AFTER INITIAL DOSE												
		1	2	3	6	24	26	28	48	50	52	72	74	76
E. D.	6	3.8	7.3	8.5	6.3	10.7	9.1	6.9	5.3	7.3	10.4	2.0	9.9	8.3
W. G.	7	15.1	14.0	11.9	4.4	6.5	6.2	7.2	2.7	3.2	5.2	0.3	3.0	6.7
R. L. H.	20	16.0	12.8	9.1	4.5	12.8	7.3	4.9	9.9	8.5	5.4	9.1	7.3	5.2
L. J.	20	20.2	19.2	15.0	7.8	12.2	7.4	5.8	10.8	8.7	5.1	3.4	2.1	1.4
R. L. H.	23	11.0	13.7	12.9	8.3	6.1	5.0	3.3	6.2	5.6	4.5	6.1	7.4	6.6
B. H.	30	11.4	14.8	12.6	6.7	3.4	3.0	1.9	2.9	5.1	5.1	2.0	2.3	2.3
M. A.	30	12.2	16.9	12.0	7.4	4.1	3.5	2.9	4.0	6.1	6.1	4.9	8.3	6.5
P. M.	30	13.5	16.7	11.1	5.8	4.2	4.7	3.5	6.1	7.4	4.5	3.9	7.7	5.1
H. W.	34	3.4	17.5	18.7	9.1	4.5	6.7	4.6	4.6	8.2	8.5	7.9	9.4	8.1
I. A.	35	12.1	19.2	12.3	4.8	3.3	6.1	4.7	3.9	8.1	5.5	9.9	8.1	5.7
Mean (10)	23.5	11.9	15.2	12.4	6.5	6.8	5.9	4.6	5.6	6.5	6.0	5.0	6.6	5.6
Range: Lowest		3.4	7.3	8.5	4.4	3.3	3.0	1.9	2.7	3.2	4.5	2.0	2.1	1.4
Highest		20.2	19.2	18.7	9.1	12.8	9.1	7.2	10.8	8.7	10.4	9.9	9.9	8.3

TABLE XI. BLOOD LEVELS OF FREE SULFONAMIDE FOLLOWING MULTIPLE ORAL DOSES OF ACETYLSULFISOXAZOLE
(100 mg. per Kilogram Initially and 50 mg. per Kilogram Every 6 Hours)

NAME	WT. (KG.)	HOURS AFTER INITIAL DOSE												
		1	2	3	6	24	26	28	48	50	52	72	74	76
H. N.	2	1.8	2.8	3.0	4.8	2.9	3.9	3.9	3.8	4.1	3.8	4.4	4.8	4.4
D. W.	5	0.5	1.7	2.6	2.6	6.0	6.5	8.3	3.6	4.7	3.7	7.1	7.1	10.1
E. R.	5	0.0	0.0	0.7	0.5	6.4	6.6	7.8	3.9	3.2	3.4	0.3	0.7	1.7
K. J.	9	1.7	2.8	5.4	5.6	2.5	2.8	6.4	4.8	--	--	--	--	--
S. J.	11	4.5	6.5	7.5	5.8	5.8	8.3	8.1	8.1	11.6	12.3	10.2	10.5	9.9
J. A.	11	7.1	8.9	8.6	4.7	6.3	5.0	4.0	5.0	5.7	4.5	4.5	5.6	5.5
R. L. H.	19	8.5	8.4	7.3	4.8	5.3	10.9	7.5	6.2	7.8	5.3	4.5	7.2	5.1
P. K.	20	6.6	5.8	5.8	5.6	10.2	10.2	9.9	10.2	4.4	5.8	5.1	8.1	7.8
R. L. H.	20	10.2	11.2	9.6	5.4	8.7	7.8	5.1	4.1	6.5	4.6	4.6	7.2	5.6
W. B.	20	--	4.4	4.1	4.1	--	4.1	4.1	4.8	5.4	4.6	2.5	3.6	3.2
L. J.	21	2.8	3.0	2.8	2.3	8.4	6.4	6.7	1.1	0.3	4.0	5.6	5.1	5.6
C. J.	26	1.3	1.4	1.5	0.7	2.3	1.1	1.1	2.7	1.7	1.3	0.7	2.5	1.5
M. P.	30	1.3	1.8	1.9	3.0	2.7	4.4	3.6	4.1	4.8	3.4	3.8	3.2	2.5
M. C.	30	2.5	2.4	1.9	1.0	3.6	2.5	1.5	4.5	4.7	3.2	3.0	4.1	3.4
H. W.	34	9.0	10.0	9.6	5.6	5.3	9.1	6.9	5.9	8.2	5.3	2.6	7.6	6.4
I. A.	35	3.9	4.5	4.0	2.0	3.8	5.7	6.4	4.6	7.0	4.0	2.6	7.1	7.7
Mean (16)		4.1	4.7	4.8	3.7	5.3	6.0	5.7	4.8	5.3	4.6	4.1	5.6	5.4
Range: Lowest		0.0	0.0	0.7	0.5	2.3	1.1	1.1	1.1	0.3	1.3	0.3	0.7	1.5
Highest		10.2	11.2	9.6	5.6	10.2	10.9	9.9	10.2	11.6	12.3	10.2	10.5	10.1

and averaged 13.9 mg. per cent. All patients exceeded a blood sulfonamide level of 7.0 mg. per cent and individual determinations ranged from 3.6 to 30 mg. per cent in this group.

Preliminary studies of sulfaethylthiadiazole suggested that a consistent level could be maintained using an initial dose of 100 mg. per kilogram

Cerebrospinal Fluid Studies.—The cerebrospinal fluid and blood concentration of free sulfonamide was determined in fifty children, following sulfonamide medication. Acetylsulfisoxazole was administered to fifteen children and the resulting blood and cerebrospinal fluid levels were measured (Table XIV). In seven children

TABLE XII. BLOOD LEVELS OF FREE SULFONAMIDE FOLLOWING THE ADMINISTRATION OF MULTIPLE ORAL DOSE OF TRIPLE SULFONAMIDE MIXTURES
(100 mg. per Kilogram Initially and 50 mg. per Kilogram Every 6 Hours)

NAME	WT. (KG.)	HOURS AFTER INITIAL DOSE												
		1	2	3	6	24	26	28	48	50	52	72	74	76
D. W.	5	7.7	8.0	8.9	8.0	15.5	14.9	12.7	--	--	--	--	--	--
D. W.	5	7.5	11.1	11.9	12.0	30.0	30.0	24.0	19.3	18.0	16.5	15.9	18.9	16.5
R. L. H.	20	1.0	17.5	16.9	12.5	11.5	12.0	10.0	11.1	14.2	10.7	12.2	13.9	10.6
L. J.	20	12.2	14.9	14.9	14.3	21.5	20.6	19.1	28.7	27.5	32.6	24.2	23.3	23.2
W. B.	20	10.1	12.6	14.9	12.9	8.2	12.0	10.7	--	--	--	--	--	--
L. J.	20	18.9	19.5	18.9	18.3	22.2	15.9	21.3	16.8	17.1	16.8	14.5	16.5	15.9
R. L. H.	20	14.8	16.6	15.4	11.0	11.8	11.8	9.1	10.0	11.4	8.8	8.2	11.0	11.0
H. W.	34	1.4	8.8	12.4	8.8	6.7	7.0	7.5	9.1	11.5	11.1	8.3	8.8	7.6
H. W.	34	5.5	11.7	12.9	9.1	7.6	8.1	8.2	6.7	11.3	10.6	3.6	4.9	6.6
I. A.	35	2.8	17.3	16.7	14.9	12.2	13.1	10.9	11.6	16.5	13.7	16.1	16.1	11.6
I. A.	35	11.3	12.0	12.7	7.4	10.5	14.7	9.9	10.8	20.1	14.7	7.2	6.8	8.7
Mean (11)		8.5	13.6	14.2	11.7	14.3	14.6	13.0	13.8	16.4	15.1	12.2	13.4	12.4
Range: Lowest		1.0	8.0	8.9	7.4	6.7	7.0	7.5	6.7	11.3	8.8	3.6	4.9	6.6
Highest		18.9	19.5	18.9	18.3	30.0	30.0	24.0	28.7	27.5	32.6	24.2	23.3	23.2

TABLE XIII. BLOOD LEVELS OF FREE SULFONAMIDE FOLLOWING MULTIPLE ORAL DOSES OF SULFAETHYLTHIADIAZOLE
(100 mg. per Kilogram Initially and 50 mg. per Kilogram Every 12 Hours)

NAME	WT. (KG.)	HOURS AFTER ADMINISTRATION												
		1	2	3	6	24	27	30	48	51	54	72	75	78
M. S.	10	8.2	8.5	6.4	6.2	10.0	10.0	6.5	10.4	12.8	13.0	7.0	13.0	12.0
J. W. P.	12	5.3	8.2	9.8	10.0	6.4	10.6	8.2	6.2	11.8	8.8	7.0	13.0	13.0
R. H.	15	4.9	8.3	11.4	10.1	3.5	11.4	7.0	3.7	12.6	10.9	3.8	13.2	7.9
L. T.	18	8.0	10.8	10.0	7.4	7.1	13.7	9.4	9.2	10.8	5.9	5.5	8.4	6.3
K. D.	26	9.0	9.6	8.2	5.1	6.1	10.9	8.4	9.4	13.3	11.5	7.6	11.7	10.9
C. B.	45	7.9	9.9	11.3	10.8	5.3	11.6	9.7	9.3	8.7	10.5	7.9	10.8	9.6
Mean (6)		7.2	9.2	9.5	8.3	6.4	11.4	8.2	8.0	11.7	10.1	6.5	11.7	10.0
Range: Lowest		4.9	8.2	6.4	5.1	5.3	10.0	6.5	3.7	8.7	5.9	3.8	8.4	6.3
Highest		8.2	10.8	11.4	10.8	10.0	13.7	9.7	10.4	13.3	13.0	7.9	13.2	13.0

followed by 50 mg. per kilogram every 12 hours (Table XIII). Six patients were studied on this schedule. Their average blood free sulfonamide level after the first 6 hours ranged from 6.4 to 11.7 mg. per cent and averaged 9.7 mg. per cent.

(Part I) who received a single oral dose of 100 mg. per kilogram of body weight, the cerebrospinal fluid and blood levels were measured 3 to 6 hours later. The mean time interval was 3.6 hours; the mean blood level of free sulfonamide was 3.8 mg. per cent, and

the mean cerebrospinal fluid free sulfonamide level was 0.6 mg. per cent. Two children received 200 mg. per kilogram of body weight acetylsulfisoxazole and after an interval of 3 to 4.5 hours, respectively, the blood sulfonamide levels were 5.8 and 5.5 mg. per cent and the corresponding cerebrospinal fluid sulfonamide levels were both 0.7 mg. per cent.

Table XIV. Level of Free Sulfonamide in the Cerebrospinal Fluid Following Oral and Parenteral Therapy With Acetylsulfisoxazole

NAME	WT. (KG.)	DOSE	HOURS AFTER LAST DOSE	BLOOD	CSF	DIAGNOSIS
Part I.	*Single Oral Doses*					
C. B.	3.5	100 mg./Kg.	3	3.9	1.7	Growth failure
A. T.	8	100 mg./Kg.	4	3.4	0.3	H. influenza meningitis
J. B.	9	100 mg./Kg.	6	4.3	0.9	Tuberculous meningitis
R. P.	10	100 mg./Kg.	3	5.4	0.7	Tuberculous meningitis
E. E.	11	100 mg./Kg.	3	2.7	0.3	Tuberculous meningitis
W. B.	19	100 mg./Kg.	3	4.1	0.0	Brain tumor-ependymoma
N. D.	41	100 mg./Kg.	3	2.7	0.3	Grand mal epilepsy
Mean			3.6	3.8	0.6	
J. B.	9	200 mg./Kg.	3	5.8	0.7	Tuberculous meningitis
W. G.	10.5	200 mg./Kg.	4.5	5.5	0.7	Guillain-Barre syndrome
Mean			3.7	5.6	0.7	
Part II.	*Multiple Oral Doses*					
H. B.	3.5	50 mg./Kg. q 6 hr. × 36	2	5.8	1.7	Streptococcal meningitis
K. J.	9	100 mg./Kg. × 1 and 50 mg./Kg. q 6 hr. × 3	6	2.5	0.0	Congenital hydrocephalus
K. J.	9	100 mg./Kg. × 1 and 50 mg./Kg. q 6 hr. × 11	4	4.8	0.3	Congenital hydrocephalus
E. E.	11	45 mg./Kg. q 6 hr. × 40	3	10.7	3.4	Tuberculous meningitis
D. A.	12	120 mg./Kg. × 1 and 60 mg./Kg. q 6 hr. × 12	5	2.8	0.2	Hydrocarbon pneumonitis
W. B.	19	100 mg./Kg. and 50 mg./Kg. q 6 hr. × 7	4	3.2	0.1	Brain tumor
Mean			4	5.0	1.0	

A multiple oral dose schedule was followed in six patients (Part II). The blood and cerebrospinal fluid levels were determined after from three to forty doses of acetylsulfisoxazole had been given. Blood and cerebrospinal fluid were obtained from analysis in from 2 to 6 hours after the last dose. The blood sulfonamide level ranged from 2.5 to 10.7 mg. per cent, with a mean of 5.0 mg. per cent. The concomitant cerebrospinal fluid levels ranged from 0.0 to 3.4 mg. per cent, with a mean of 1.0 mg. per cent.

Twenty-one children received sulfisoxazole (Table XV) following which blood and cerebrospinal fluid free sulfonamide levels were measured. Part I consists of six children in whom the blood and cerebrospinal levels were measured 3 hours after an oral dose of 100 mg. per kilogram of sulfisoxazole. The blood levels of free sulfonamide were 7.8 to 12 mg. per cent, with a mean of 10 mg. per cent, while the cerebrospinal fluid levels were 0.0 to 0.4 mg. per cent, with a mean value of 0.3 mg. per cent. Two children, after receiving multiple oral doses of sulfisoxazole (Part II), showed blood levels of 6.9 and 9.1 mg. per cent two hours after medication, and the corresponding cerebrospinal fluid levels were 0.3 to 0.7 mg. per cent. Nine

TABLE XV. LEVEL OF FREE SULFONAMIDE IN THE CEREBROSPINAL FLUID FOLLOWING ORAL AND PARENTERAL THERAPY WITH SULFISOXAZOLE

NAME	WT. (KG.)	DOSE	HOURS AFTER LAST DOSE	BLOOD	CSF	DIAGNOSIS
Part I.	*Single Oral Doses*					
E. D.	5.5	100 mg./Kg. × 1	3	8.5	0.3	Growth failure
E. D.	5.5	100 mg./Kg. × 1	3	12.0	0.4	Growth failure
W. G.	7	100 mg./Kg. × 1	3	11.9	0.4	Hypochromic anemia
W. G.	7	100 mg./Kg. × 1	3	7.9	0.0	Hypochromic anemia
G. S.	10	100 mg./Kg. × 1	3	7.8	0.3	Lung abscess
T. H.	65	100 mg./Kg. × 1	3	12.0	0.2	Hypocalcemia
Mean				10.0	0.3	
Part II.	*Multiple Oral Doses*					
E. D.	5.5	100 mg./Kg. × 1 and 50 mg./Kg. q 6 hr. × 7 p.o.	2	9.1	0.7	Growth failure
W. G.	7	100 mg./Kg. × 1 and 50 mg./Kg. q 6 hr. × 7 p.o.	2	6.2	0.3	Hypochromic anemia
Mean				7.7	0.5	
Part III.	*Single Intravenous*					
E. D.	5.5	100 mg./Kg. × 1	1	16.4	1.3	Growth failure
W. G.	7	100 mg./Kg. × 1	1	12.7	1.7	Hypochromic anemia
J. B.	10	100 mg./Kg. × 1	1	15.0	1.8	Tuberculous meningitis
R. C.	12	100 mg./Kg. × 1	1	13.6	1.4	Tuberculous meningitis
Mean				14.4	1.6	
E. D.	5.5	100 mg./Kg. × 1	3	23.2	8.1	Growth failure
W. G.	7	100 mg./Kg. × 1	3	10.9	1.0	Hypochromic anemia
R. B.	8	100 mg./Kg. × 1	3	22.6	21.3	Purulent meningitis
J. B.	10	100 mg./Kg. × 1	3	18.6	0.3	Tuberculous meningitis
R. C.	12	100 mg./Kg. × 1	3	10.9	1.5	Tuberculous meningitis
Mean				19.4	6.4	
Part IV.	*Other Parenteral*					
J. T.	5	100 mg./Kg. × 1	4.5	8.8	0.3	Purulent meningitis
E. C.	6	100 mg./Kg. × 1	3	8.8	3.6	Streptococcal meningitis
D. H.	65	200 mg./Kg./day I. V. cont. drip	3 da.	36.9	28.5	Pneumococcal meningitis
Mean				18.1	10.8	

TABLE XVI. LEVEL OF FREE SULFONAMIDE IN THE CEREBROSPINAL FLUID FOLLOWING ORAL AND PARENTERAL THERAPY WITH SULFADIAZINE

NAME	WT. (KG.)	DOSE	HOURS AFTER LAST DOSE	BLOOD	CSF	DIAGNOSIS
F. C.	25	100 mg./Kg. × 1 p.o.	3.5	0.7	0.3	Cerebral palsy-birth-injury
J. B.	10	200 mg./Kg. × 1 p.o.	4.5	7.0	0.5	Tuberculous meningitis
R. C.	12	200 mg./Kg. × 1 p.o.	4.5	6.2	2.3	Tuberculous meningitis
O. H.	12.5	50 mg./Kg. S.Q. q 6 hr. × 6	3	26.1	9.5	Meningococcus meningitis
E. C.	6	100 mg./Kg. S.Q. × 1 and 50 mg./Kg. S.Q. q 6 hr. × 7	2	25.8	22.2	Streptococcal meningitis
G. W.	8	200 mg./Kg./day I. V. by cont. drip	15 (after start)	17.4	9.2	*H. influenzae* meningitis
E. W.	20	100 mg./Kg. × 1 I. V.	3.5	28.8	9.6	Meningococcus meningitis

children (Part III) received sulfisoxazole 100 mg. per kilogram intravenously. In four patients studied 1 hour later the blood levels ranged from 12.7 to 16.4 mg. per cent, with a mean of 14.4 mg. per cent. The cerebrospinal fluid levels ranged from 1.3 to 1.8 mg. per cent, with a mean value of 1.6 mg. per cent. Five more patients were studied 3 hours after intravenous medication and found to have blood levels of 10.9 to 33.6 mg. per cent, with a mean of 19.4 mg. per cent. The corresponding cerebrospinal fluid values ranged from 0.3 to 21.3 mg. per cent. Two patients (Part IV) received the same dose (100 mg. per kilogram) of sulfisoxazole intramuscularly. Three and 4.5 hours later the blood levels were both 8.8 mg. per cent, and the cerebrospinal fluid levels were, respectively, 0.3 and 3.6 mg. per cent. A third patient with pneumococcal meningitis received 200 mg. per kilogram per day of sulfisoxazole as a continuous intravenous infusion for a period of three days. Levels obtained during the third day of treatment revealed a blood level of 36.9 mg. per cent and a cerebrospinal fluid level of 28.5 mg. per cent.

The blood and cerebrospinal fluid levels of free sulfonamide following sulfadiazine administration were studied in seven patients (Table XVI). Following 100 mg. per kilogram orally in one patient a blood level of 0.7 mg. per cent and a cerebrospinal fluid level of 0.3 mg. per cent, were found after an interval of 3.5 hours. Two patients (J. B., R. C.) received 200 mg. per kilogram orally and demonstrated blood levels of 7.0 and 6.2 mg. per cent at 4.5 hours with corresponding cerebrospinal fluid levels of 0.5 and 2.3 mg. per cent. Two additional patients (O. H., E. C.) received sulfadiazine subcutaneously. Blood and cerebrospinal fluid free sulfonamide levels 3 and 2 hours after the last dose were 26.1 and 25.8 mg. per cent in the blood and 9.5 and 22.2 mg. per cent in the cerebrospinal fluid. A patient (G. W.) was given a continuous intravenous infusion of 200 mg. per kilogram per day of sulfadiazine. Specimens of blood and cerebrospinal fluid obtained 15 hours after the start of the infusion revealed a blood level of 17.4 mg. per cent and a cerebrospinal fluid level of 9.2 mg. per cent. One additional patient (E. W.) received a single intravenous dose of 100 mg. sulfadiazine per kilogram and 3.5 hours later had a blood level of 28.8 mg. per cent and a cerebrospinal fluid level of 9.6 mg. per cent.

No complications of sulfonamide therapy were encountered in the course of these studies.

DISCUSSION

Successful chemotherapy of infections with sulfonamide preparations depends in part upon the physician's knowledge of the properties of sulfonamides generally as well as the pharmacodynamic properties of the individual drug prescribed. Thus route of administration, rate and degree of absorption, metabolism, and excretion must be known if the proper sulfonamide is to be selected.

Sulfonamide preparations are not destroyed by the enzymes of the gastrointestinal tract though acetylated forms may be split before absorption. The sodium salts are highly soluble and may be administered parenterally in from 0.5 to 5 per cent solutions. Solutions in the lowered concentration

range are preferable in that they ensure adequate water intake and can be given over long periods to maintain therapeutically effective blood levels.

Following absorption sulfonamide compounds exist in the blood in three states, the quantity existing in a given moiety varying with the preparation being studied. A variable portion is bound to blood proteins, another portion is acetylated, and the remainder exists as the therapeutically active free sulfonamide. The protein bound form has no chemotherapeutic activity and in most instances the acetylated form has no antimicrobial activity. The one exception to this is the modest antibacterial effect of acetylsulfisoxazole.

For these reasons total blood sulfonamide levels are of little interest to the physician and it is customary to determine only the free sulfonamide present. This is fortunate since the determination of total blood sulfonamide is a much more complicated procedure. The specimen must first be ashed to liberate the protein-bound fraction, submitted to acid hydrolysis to free the conjugated sulfonamide, and finally a standard diazo reaction is carried out to measure quantitatively the free and liberated sulfonamides. In practice this determination is rarely carried out since the therapeutically active moiety is the more readily measured free sulfonamide which is reported as milligrams per cent of the sulfonamide being administered or, in the case of a triple sulfonamide mixture, as milligrams per cent of triple sulfonamides.

The excretion of sulfonamides in the urine is largely as the acetylated form, a somewhat unfortunate circumstance since for most sulfonamides this form is slightly less soluble at urinary pH than is the free form. The exception to this is the conjugate of sulfadiazine, which is slightly more soluble than free sulfadiazine.

To this point little has been said concerning the chemotherapeutic properties of sulfonamides. In the introduction it was mentioned that some of the earlier sulfonamides appeared to show individual variations in their antibacterial spectrum. However, all of the sulfonamides now in general use show a similar range of therapeutic effectiveness. The use of the rapid in vitro disk methods for the determination of bacterial sensitivity to a sulfonamide has led to some confusion in this respect. The in vitro determination of sensitivity or resistance of bacterial organisms to antibiotic preparations has gained widespread popularity and often represents a determination essential to correct selection of the antibiotic. While the tube dilution method for antibiotic sensitivity determination is more reliable, the much more readily carried out disk sensitivities have sufficient accuracy to be very useful, particularly if disks representing several concentrations of the antibiotic agent are used. In most instances the antibiotic spectrum of the offending bacterial organism can be determined at the time of the original culture. This method of testing has been used but is not as useful for sulfonamide preparations because of the many sulfonamide inhibitors present in ordinary laboratory media. It is essential in performing precise sulfonamide sensitivities that the media be prepared with special precautions to exclude sulfonamide inhibitors and that the sulfonamide to be tested be incorporated into the media. For these

reasons information as to the sensitivity of sulfonamides to a particular microorganism is less readily available and often less reliable. Thus in the presence of an organism known to be sensitive to a sulfonamide generally, preference for a particular preparation is based more upon pharmacodynamic properties rather than upon bacteriologic specificity.

Sulfonamides act only as bacteriostatic agents, through competitive inhibition of para-aminobenzoic acid utilization. Response of clinical symptomatology to therapy with sulfonamides is usually less rapid than to antibiotic agents. This difference is probably due to the more rapid antibacterial effect of the antibiotics.

For the reasons stated it is clinically useful to study the blood levels of free sulfonamide as this represents the quantity of therapeutically active sulfonamide in this body fluid. A dose of 100 mg. per kilogram of body weight was selected for study since it represents a commonly used initial dose. Fig. 1 is a composite graph of the average sulfonamide levels following a single oral dose of eight of sulfonamide preparations as determined over a 24-hour period of observations. The sulfadiazine curve is emphasized by a heavy line since it represents the sulfonamide with which physicians generally have had the greatest experience and the drug whose therapeutic efficacy is most clearly established. It is immediately apparent that all of the other sulfonamides studied are more rapidly absorbed and show an earlier peak blood level. In this comparable dose study, however, sulfamethylthiadiazole and acetylsulfisoxazole reach peak levels of only 6 mg. per cent, less than that of sulfadiazine. The high solubility of sulfamethylthiadiazole leads to a rapid fall in its blood level and indicates that blood levels are difficult to maintain on any of the usual dosage schedules. However, its rapid excretion makes it efficacious in the treatment of urinary tract infections and it has found its principal use for this purpose. It is not a recommended therapeutic agent in circumstances where hematogenous spread of the urinary infection is present or anticipated.

Acetylsulfisoxazole in aqueous suspension is slowly absorbed, but this defect has been successfully overcome by the preparation of stable lipid emulsions which give 20 to 30 per cent higher blood levels than a comparable dose of the aqueous suspension. Sulfisomidine is rapidly absorbed but it, too, shows unusually rapid excretion and is not an ideal chemotherapeutic agent for the treatment of infections where maintenance of blood levels is desired. Sulfisoxazole shows rapid absorption and only moderately rapid fall in blood level; it can therefore be depended upon for sustained blood levels when given at 6- to 8-hour intervals, and its high solubility at the usual urinary hydrogen ion concentration explains the virtual absence of renal complications.

Sulfaethylthiadiazole was administered in a modified aqueous suspension. Its curve reveals good absorption and sustained blood levels such that a 12-hour dosage interval is sufficient to assure sustained blood levels. Clinical experience in this country is limited but early reports and reports from the European literature suggest that its chemotherapeutic range is similar to that of sulfadiazine.

A triple sulfonamide mixture studied was composed of equal parts of sulfadiazine, sulfamerazine, and sulfamethazine. The 24-hour blood levels reveal the rapid absorption and high peak characteristic of both sulfamethazine and sulfamerazine plus the sustained blood level characteristic of sulfadiazine. Low renal toxicity in association with easily maintained blood levels have given the triple sulfonamides widespread chemotherapeutic popularity.

Table XVII. A Recommended Schedule of Dosage for Oral Sulfonamide Therapy in Children

Drug	Form	Dose mg./kg.		
		Initial	Maintenance	Frequency
Sulfadiazine	Tablets 0.5 Gm.	100	50	q 6 h
	Aq. susp. 0.5 Gm./4 c.c.	100	50	q 6 h
	Lipo. susp. 0.5 Gm./4 c.c.	100	50	q 8 h
Sulfisoxazole	Tablets 0.5 Gm.	100	50	q 6 h
Acetylsulfisoxazole	Aq. susp. 0.5 Gm./4 c.c.	100	50	q 6 h
	Lipo. susp. 0.5 Gm./4 c.c.	100	50	q 8 h
Triple sulfonamides	Tablets 0.5 Gm.	70	50	q 8 h
	Aq. susp. 0.5 Gm./4 c.c.	70	50	q 8 h
	Lipo. susp. 0.5 Gm./4 c.c.	100	50	q 12 h
Sulfamethylthiadiazole	Aq. susp. 0.25 Gm./5 c.c.	*50	25	q 6 h
Sulfisomidine	Aq. susp. 0.25 Gm./4 c.c.	*50	25	q 6 h
Sulfaethylthiadiazole	Aq. Spansule susp. 0.65 Gm./4 c.c.	100	50	q 12 h

*Dose for lower urinary tract infections.

Sulfamethoxypyridazine is a recently developed sulfonamide that has the interesting properties of excellent and rapid absorption, a low rate of acetylation and an extremely high rate of renal tubular reabsorption. These qualities combine to give high, long-sustained blood levels of free sulfonamide following single oral doses. Its chemotherapeutic range is said to be similar to that of other sulfonamides but final evaluation of it as a therapeutic agent will await further clinical experience. The sustained blood levels suggest it may potentially be particularly valuable as a prophylactic drug.

Multiple oral dose studies were carried out on the five drugs likely to be used in this manner. The mean data of Tables IX to XIII were used in preparing Fig. 3 for the purpose of graphically demonstrating the rate and degree of absorption as well as the average blood sulfonamide level over a three-day period. The dose schedule was 100 mg. per kilogram of body weight initially and 50 mg. per kilogram of body weight for the maintenance dose. An interval of six hours between doses was used for all but sulfaethylthiadiazole, where a 12-hour interval was employed.

The quantity of a sulfonamide compound entering the cerebrospinal fluid in comparison to its blood level can be used as one indication of its ability to penetrate the tissues and body fluids. Cerebrospinal fluid obtained by lumbar puncture was therefore evaluated for free sulfonamide content following the administration of single, multiple, oral,

and parenteral doses of three sulfonamide preparations. The observations in Tables XIV to XVI immediately suggest that parenteral administration of sulfonamides is the most efficient route for the rapid production of high cerebrospinal fluid levels, even in patients with inflammatory central nervous system diseases, such as purulent meningitis.

Table XVII is a schedule of suggested initial and maintenance dosage for the sulfonamides studies. The doses given are planned to give blood levels from 6 to 10 mg. per cent on the basis of the studies reported here. Since one of the prime indications for sulfonamides is meningococcal meningitis, the availability of parenteral preparations for therapy is an important consideration. Only sulfadiazine and sulfisoxazole are available generally in form for parenteral administration.

CONCLUSION

1. On the basis of the information obtained in this study, it would seem that there are no signifiant differences between sulfisoxiazole, the triple sulfonamide mixtures, and sulfaethylthiadiazole in the production of levels usually considered to be bacteriostatic for the management of systemic infections due to susceptible organism provided that slight differences in absorption are compensated for by differences in doses.

2. The oral administration of lipid suspension of acetylsulfisoxazole, sulfadiazine, and triple sulfonamides produce higher levels than those obtained following the use of aqueous suspensions of the same drug.

3. One drug sulfaethylthiadiazole in Spansules suspension was administered every 12 hours and was found to produce high and sustained levels.

4. Because of the rapid excretion of sulfamethylthiadiazole and sulfisomidine, it is more difficult to maintain levels usually considered necessary for the treatment of systemic infections.

5. There is considerable variation in the diffusion of the various sulfonamides into the cerebrospinal fluid, but levels were strikingly higher following parenteral administration.

6. Studies with a new sulfonamide, sulfamethoxypyridazine, revealed levels in the therapeutic range 36 hours following the ingestion of a single oral dose.

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Of Terrible Dreames and Feare in the Slepe

Oftentimes it happeneth that the chyld is afraid in the slepe, & somtymes waketh sodainly, & sterteth, somtyme shriketh and trembleth, whiche effect commeth of the arysing of stynkyng vapours out of the stomacke into the fantasye, and sences of the brayne, as ye maye perceyve by the breath of the chylde: wherfore it is good to geve hym a litle hony to swallow, and a lytle pouder of the seedes of peonie, and sometimes triacle, in a litle quantitie with mylke, and to take hede that the chylde sleepe not with a full stomake, but to beare it about waking, tyl part be digested, and whan that it is layde, not to rocke it muche, for overmuche shaking letteth digestion, and maketh the childe many tymes to vomyte.

THOMAS PHAIRE'S THE BOKE OF CHYLDREN, 1544.

THE COMPARATIVE ANTIPYRETIC EFFECT OF N-ACETYL-P-AMINOPHENOL AND ACETYLSALICYLIC ACID

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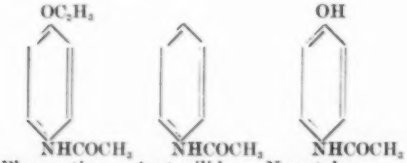
THE ever-present problem of the child with fever continues to harass the practitioner as he seeks a safe and effective method to alleviate this symptom. In this paper we wish to report a series of 100 children with fever treated on an alternate-patient basis with two antipyretic agents: a relatively new agent, an elixir form of N-acetyl-p-aminophenol and acetylsalicylic acid. The purpose of this study was to compare the antipyretic effectiveness of N-acetyl-p-aminophenol (Tylenol)* and acetylsalicylic acid (aspirin).

CHEMISTRY AND PHARMACOLOGY

N-acetyl-p-aminophenol is the principal metabolite of both acetanilid and phenacetin. The structural relationship between these three compounds is shown below:



Phenacetin — Acetanilid — N-acetyl-p-aminophenol

When either acetanilid or phenacetin is given, one can recover from the urine 90 per cent of the administered dose of N-acetyl-p-aminophenol which is almost entirely present as a hydroxyl conjugate.[1] This finding stimulated investigation to determine: (1) the toxicity of this metabolic excretory form, and (2) its antipyretic analgesic properties. It has been established in both experimental animals and man that there is complete absence of such toxic properties as methemoglobinemia, anemia, agranulocytosis, and liver damage, all of which have been reported following the use of acetanilid or phenacetin.[2-5] It has been found to be as antipyretic as acetanilid, but less analgesic.[1] Others have found the analgesic effect to be comparable to that of acetanilid.[6]

N-acetyl-p-aminophenol is a stable substance and undergoes no breakdown, either alone or in combination with aspirin or caffeine.

METHOD OF STUDY

Each drug was given on an alternate-patient basis to 100 patients of pediatric age range who were seen in the outpatient clinic with a temperature elevation of 102° F. (R) or higher. The primary diagnoses of the two groups were as follows:

	Tylenol	*Aspirin*
Pneumonia	10	12
Pharyngitis	8	9
Rubeola	9	9
Diffuse URI	4	5

From the Pediatric Outpatient Service, Jefferson Davis Hospital, and the Department of Pediatrics, Baylor University College of Medicine.

*Tylenol, supplied by McNeil Laboratories Inc., Philadelphia, Pa.

Bronchitis	2	3
Otitis media	5	3
Herpetic stomatitis	2	2
Roseola infantum	2	1
Bronchiolitis	1	1
Gastroenteritis	1	1
Varicella	1	
Sinusitis		1
Aseptic meningitis	1	
Cellulitis	1	
Fever of undetermined origin	3	3
Total	50	50

The degree of temperature elevation before treatment and the ages of the two groups are correlated in Table I. It can be seen that the two groups are essentially comparable, except that the Tylenol group contains a higher percentage of patients under 1 year of age. The great majority of these patients, however, did not have the very high temperatures which classically respond so well to antipyretic agents.

The dosage of aspirin was 65 mg. per year of age. It was given as an orange-flavored tablet which was crushed in water if the child was too young to swallow it. The dosage of Tylenol was 60 mg. (½ teaspoonful) for infants under 1 year of age, 120 mg. (one teaspoonful) for children 1 to 4 years of age, and 240 mg. (two teaspoonfuls) for children over 4 years. Tylenol was supplied as a cherry-flavored elixir.

Rectal temperatures were recorded on each child at one-half, one, two, three, four, five, and six hours after drug administration unless there was evidence that the antipyretic effect had subsided prior to six hours. No specific medication was given until after the study had ended.

TABLE I. DISTRIBUTION OF PATIENTS WITH RESPECT TO AGE AND ORIGINAL TEMPERATURE

AGE (YR.)	102-102.9°		103-103.9°		104-104.9°		105° AND OVER	
	TYL.	ASA	TYL.	ASA	TYL.	ASA	TYL.	ASA
0-1	5	0	6	1	2	4	1	1
1-2	4	7	6	4	5	7	1	2
2-3	0	0	2	3	1	2	0	0
3-4	2	1	2	2	1	1	1	0
4-5	0	1	1	2	1	2	0	1
5-6	0	1	1	1	1	0	0	0
Over 6	3	2	4	3	0	2	0	0

TABLE II. REPRESENTATIVE "PER CENT OF ORIGINAL TEMPERATURE" USED TO COMPARE ANTIPYRETIC DRUGS

TIME FOR DRUG ADMINISTRATION (IN HR.)	RECTAL TEMPERATURE (F.)	PER CENT OF ORIGINAL TEMPERATURE
0 (before drug)	104	104 /104—100 %
½	102.6	102.6/104— 98.7%
1	101.8	101.8/104— 97.9%
2	100	100 /104— 96.2%
3	99.6	99.6/104— 95.8%
4	100	100 /104— 96.2%
5	100.2	100.2/104— 96.3%
6	102	102 /104— 98.1%

TABLE III. COMPARATIVE EFFECT OF TYLENOL AND ASPIRIN ON HYPERTHERMIA
Average for Fifty Patients Receiving Single Oral Doses of Each

TIME AFTER DRUG ADMINISTRATION (IN HOURS)	PER CENT OF ORIGINAL TEMPERATURE	
	ASPIRIN	TYLENOL
½	99.6	99.3
1	99.2	98.4
2	98.1	97.5
3	97.7	97.3
4	97.8	98.3
5	98.5	98.9
6	99.1	99.2

RESULTS

Comparative Antipyretic Effect.—The drop in temperature for each time period was calculated as "per cent of original temperature." A representative record is shown in Table II.

The average fall in temperature for each time period for the two groups receiving aspirin or Tylenol is shown in Table III.

The data presented graphically in Fig. 1 indicate that Tylenol produced a definite decrease in body temperature and that this drug was at least as effective as aspirin. The over-all decrease in body temperature during the first three hours after administration of the drugs was greater with Tylenol than with aspirin. The duration of maximum antipyretic effect with Tylenol was somewhat shorter than with aspirin. These differences are not statistically significant.

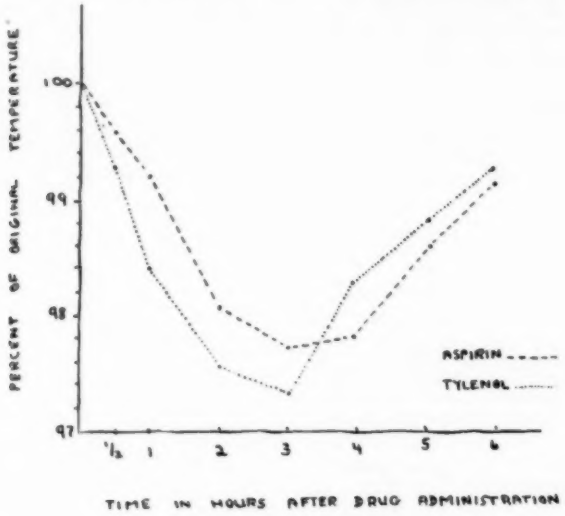


Fig. 1.

Acceptability.—In pediatric practice, acceptability of a drug by the patient is of considerable importance. An attempt to grade the acceptability of Tylenol as compared to aspirin resulted in the data summarized in Table IV. The acceptability was graded as *good* if medication was taken readily; *fair,* if taken with protest; and *poor,* if forced or "poured down" the child with active coercion. On this basis both drugs were essentially equal since the acceptability was classified as "good" in thirty-seven patients (74 per cent) of each group.

TABLE IV. CLINICAL ACCEPTABILITY OF TYLENOL AND ASPIRIN

	TYLENOL	ASPIRIN
Good	37	37
Fair	4	8
Poor	9	5

Side Effects.—No clinical side effects with either Tylenol or aspirin were observed in this phase of the study. The patients received only a single dose of either drug which did not provide a valid basis for comparison of two well-tolerated preparations.

In order to determine the side effects associated with prolonged administration of Tylenol, a group of ten patients received the drug in therapeutic amounts four times a day for a two-week period. No clinical side

effects were observed during this period and there were no differences noted between the pre-treatment and post-treatment blood counts, urinalyses, or liver function tests. These results are in agreement with those of Cornely and Ritter[7] who found that Tylenol had no effect on hematologic, renal, or hepatic function.

SUMMARY AND CONCLUSIONS

1. A clinical technique utilizing rectal temperatures in 100 febrile children has been used to compare the antipyretic effect of an elixir form of N-acetyl-p-aminophenol (Tylenol) with acetylsalicylic acid (aspirin).

2. This technique utilizes a number representing a "per cent of original temperature" to quantitate the drug effect at a given time.

3. The antipyretic effects of Tylenol and aspirin are essentially the same.

4. The maximum antipyretic effect with both Tylenol and aspirin is reached at three hours. The onset of action occurs somewhat earlier with Tylenol than with aspirin, but the duration of effect is shorter.

5. The acceptability of Tylenol and aspirin are approximately equal.

6. No clinical side effects or changes in blood counts, urinalyses, or liver function tests were observed as the result of the administration of Tylenol four times a day for two weeks to a group of ten children.

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ANOXIA AS A SIGNIFICANT PERINATAL EXPERIENCE: A CRITIQUE

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WE HAVE recently reported several studies of neonates in which an attempt has been made to determine relationships among three variables: the perinatal history, the performance on behavioral tests, and oxygen saturation of the blood. These studies were undertaken as part of a larger project concerned with the likelihood that certain early experiences will lead to later defects in development and, specifically, whether anoxia is such an experience.

Interest in this problem arises from a desire to find the origin of many kinds of defects, ranging from severe, crippling handicaps, such as cerebral palsy, epilepsy, or mental retardation, to less obvious or special defects, like deafness, reading disability coupled with normal intelligence, some forms of behavior disorder, and so on. These defects have in common that they are not wholly or satisfactorily accounted for either by genetic factors or as reactions to the psychological environment. Another possible causative factor is that of brain injury. This is a broad concept which, to account for such diverse phenomena, must include gross and minimal, localized as well as diffuse injury. When extended in this way, the concept goes beyond the realm of established relationships between gross brain injury and function to the postulating of injury so minimal as to leave no palpable neurological residual but yet able to affect the adaptive capacity of the child. Gesell has been one of the strongest advocates of this position and has stated that there is a "sizeable group of cases . . . that could only be accounted for on the basis of mild or resolving injury."[1, p. 231]

A difficulty in using brain injury as an explanation of defects not otherwise accounted for is that numerous children possess these defects who have never been exposed to an identifiable and unequivocal source of injury, such as a brain tumor, lead poisoning, etc. It has been hypothesized that such children suffer undetected injury during infancy or the prenatal period, a period when it is difficult to assess the consequences to the central nervous system of any kind of trauma. Referring to the totality of possibly injurious experiences which can occur

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during pregnancy, birth, and the neonatal period, Lilienfeld and co-workers[2] have postulated a "continuum of reproductive casualty," a continuum of experiences ranging in their severity and leading to effects which also vary in degree. The experiences which are incriminated by their studies are "those that result in anoxia or nonmechanical injury, rather than those that result in mechanical injury."[1, p. 641]

Other considerations also focus attention on perinatal anoxia as a possibly important source of later defects. While birth injury, in the sense of injury due directly to mechanical forces, unquestionably can cause serious damage, with modern obstetrical procedures it is a relatively rare phenomenon. A reduction in oxygen, on the other hand, does occur frequently. From 5 to 10 per cent of newborn infants have difficulty in establishing respiration after birth, and an unknown number have been exposed to oxygen reduction during fetal life. Further, there is ample experimental evidence to indicate the consequences upon cellular development of marked deviation in oxygen supply. Because the effects of anoxia on the brain are highly variable, it could account for widely varying behavioral consequences.[3]

Opinions differ, however, as to whether or not perinatal anoxia has any residual effects. There are those who, while acknowledging that it may be the cause of death, imply that if the infant recovers at all, he recovers completely and without later effects.[4, 5] This position has been bolstered by the studies of Himwich and his group,[6] which demonstrate that the fetal and neonatal animal can withstand degrees of oxygen deficit which would be fatal to an older organism. While this suggests a relative invulnerability of the young, it does not force the conclusion that there are no gradations in response—that anoxia is either lethal or has no lasting effects. There are, in fact, other animal studies which suggest just the opposite—that, at least in some species, perinatal anoxia can produce adult animals with impaired adaptive capacity even in the absence of obvious neurological defects.[7-9] In brief, neither logical arguments nor evidence from animal studies is compelling, and the question of whether the possibly injurious experiences which do occur to the perinatal infant have lasting effects remains to be answered by research on the human organism.

A large number of studies have been designed to answer this question, but their results are conflicting. One approach has been to ascertain the birth history of groups with known defects, such as cerebral palsy, mental deficiency, epilepsy, etc.[2, 10-17] Such studies have generally reported a significantly higher frequency of apnea, difficult deliveries, or other perinatal complications than would be expected in the total population or than occurred in control groups. Many of these studies have been criticized on the grounds of poor technique, especially in the obtaining of reliable birth information. The objection could not, however, be so readily applied to the recent and extensive work reported by Lilienfeld and associates,[2, 15-17] in which only hospital records have been utilized.

In spite of recent improvements in methodology in such studies, the criticism could still be made that they do not answer the question of outcome for

a group of anoxic children. Accordingly, in recent years there has been a methodological preference for studies which begin with a documented birth record and continue by following the child's development.[4, 18-25] These studies have shown relatively little agreement with one another. Darke and Preston,[19, 20] for example, were impressed with the apparent causative relationship of neonatal apnea to defect in a high percentage of the individuals they studied. Several large-scale studies, however,[4, 22, 23, 25] have concluded that there is no significant difference between anoxic and control groups. The agreement among these latter studies, done independently and using careful methodology, is impressive. It is difficult to accept their negative results as conclusive, however, in view of both the animal work and the conflicting results obtained with human subjects. It seems worth while to consider briefly four possible explanations of the discrepant conclusions in terms of differences in (1) direction of approach to the problem, (2) criteria of later impairment, (3) use of control groups, and (4) criteria of early anoxia.

SOURCES OF DISCREPANCY

Approach to the Problem.—Part of the explanation may lie in the difference in approach, whether starting from groups with known defects or from the birth history. These represent, respectively, *retrospective* and *prospective* designs. Although these two approaches are certainly related to one another, the fact that not only are they asking different questions but also that different results would be anticipated seems to be overlooked. To ask how frequently perinatal complications may be associated with a certain defect and to ask how frequently a certain defect is associated with perinatal complications is not the same thing.

Lilienfeld and co-workers,[2, 15, 16] using a retrospective design, found that, of an epileptic group and of a mentally deficient group, approximately 15 per cent had a history of abnormal neonatal conditions and that a much higher percentage had a history of complications during pregnancy. They concluded that these factors, while not the only etiological ones, "appear to be rather influential," and they postulated a "continuum of reproductive casualty" which, for a certain proportion of cases, results in "sublethal injury which would be manifested as organic damage to the brain."[2, p. 641] In contrast, Keith and associates,[4] using the prospective approach, found that only 4 per cent of a group with neonatal asphyxia exhibited abnormalities, including convulsions and mental retardation, when examined during early childhood. A nonasphyxic control group exhibited 3 per cent of such abnormalities. They concluded that there was no evidence "that asphyxia caused any neurologic abnormality in those infants who survived."[4, p. 147]

If we disregard control groups for the moment, we may ask whether the results in these two studies are sufficiently different to justify such opposed conclusions. Because neonatal complications are found in 15 per cent of a defective group, the converse does not automatically follow, i.e., that 15 per cent of a neonatally complicated group will be defective. We can, in fact, on the basis of other information, anticipate that it will be found with considerably less frequency. Consider,

for example, the case of mental retardation. We know that approximately 2 per cent of the population is mentally retarded. If we accept Pasamanick and Lilienfeld's finding that 15 per cent of a mentally retarded group also have neonatal complications, we would expect the percentage of individuals in the total population with both mental retardation and neonatal complications to be 15 per cent of 2 per cent, or only 0.3 per cent. The percentage of neonatally complicated infants who will be retarded will depend upon how frequently neonatal complications occur. For example, if in the total population they occur with a frequency of only 0.3 per cent, then, of course, the 0.3 per cent of the population which has both neonatal complications and mental retardation would constitute 100 per cent of the neonatally complicated infants. In the Keith, Norval, and Hunt study, however, asphyxiated infants occurred with a frequency of 5 per cent. The 0.3 per cent of the population having both neonatal complications and mental retardation would, in this case, be only 6 per cent of the neonatally complicated sample. These relationships are diagramed in Fig. 1.

In choosing these particular figures for illustrative purposes, we realize that many factors have been ignored, including differences in defining neonatal complications and differences in identifying retardation, but they serve to illustrate the main point: the frequency with which a defect can be expected to occur in any defined sample will depend upon how frequently both the defect and the characteristics of the sample occur in the total population. Even if all mentally retarded children had been anoxic at birth, there would still remain many nonretarded anoxic children, as mentally

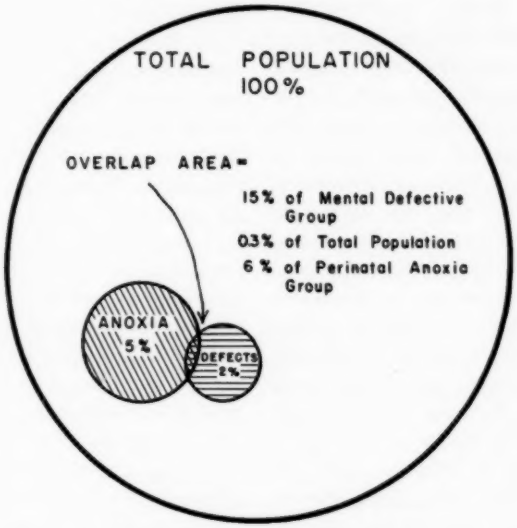

Fig. 1.—Relationships among subgroups in the population. Illustrative areas of the figure are approximate, not exact.

retarded children would constitute only 40 per cent of an anoxic group when one baby out of every twenty is anoxic. This not only has implications for interpretation of results but also is of great importance in planning research, since it is more difficult to establish a significant difference between control and experimental groups if positive findings are to be expected in only a small percentage of the total group.

Criteria of Later Impairment.—Studies have also differed in the criteria of later impairment employed. Animal research and research on the effects of anoxia in adult human subjects have measured impairment in abilities thought to be easily disrupted by brain injury, like the ability to discriminate and to learn. Studies of the effects of anoxia on the human infant, however, have been confined to relatively gross neurological defects and to general intelligence. With few exceptions they have not measured the kinds of defects which characterize children thought to be brain-injured and which could be responsible for reading difficulties, unmanageable personality patterns, and other phenomena possibly associated with minimal brain damage. While there are few adequate methods of measuring such defects in young children, we cannot conclude that early anoxia fails to produce them unless they are measured. An exception to the above generalization is a study by Rosenfeld and Bradley[14] which considered the presence or absence of six traits, including hypermotility and impulsiveness. Although the study could be criticized on several points, it is interesting that when ratings of such traits were employed, there was a marked difference between groups with and without histories of early anoxia. Similarly, a study by Stevenson[21] found that infants whose neonatal conditions differed also differed in their over-all "adjustment" as older children.

Control Groups.—The use of control groups is another crucial aspect which must be considered in evaluating effects of perinatal experiences. Most of the recent studies in this field have realized the necessity for controls but have not taken care to determine that control and anoxic groups are equated for all other variables which might themselves be associated with impairment. This is especially important when an early experience is judged by its effect several years later, by which time many other variables have had an opportunity to dilute the relationship. Results may either be invalidated or they may be obscured because differences between groups are insignificant as compared with the variability within groups. Such variability may be removed by statistical analysis, but the research must be planned to allow for this. The method, used by Darke,[19] of pairing anoxic subjects with sibling or parent controls affords one such solution.

The experimenter has a good deal of ground to cover when he attempts to equate control and experimental groups, and the task may appear hopeless if he attempts to include every conceivable variable. Campbell and associates,[22] for example, who gave careful consideration to this problem, determined whether their experimental and control groups were equated for eleven variables. Despite this, they did not mention the variable which

might be considered most important—the presence or absence of other kinds of complications or trauma which might in themselves affect a child's developmental progress, such as congenital or hereditary defects, blood incompatibilities, etc. In the Keith, Norval, and Hunt[4] study both control and asphyxiated groups included cases of monogolism, erythroblastosis, and other major complicating factors. It is not clear whether these same subjects are among those found to be abnormal in later years, but their contribution to the results cannot be considered a minor one, especially when we have reason to expect later abnormalities in only a small per cent of the anoxic group.

Criteria of Early Anoxia.—This is a question which we have dealt with in some detail in an earlier paper.[26] Anoxia is an inferred condition—an inadequate supply or use of oxygen—which has no unambiguous definition, since what is inadequate cannot be precisely specified. Three approaches have been used in the various studies. The most precise and direct method has been to measure the oxygen content of the blood. A second approach, and the most commonly used one, defines anoxia in terms of certain clinically recognized disturbances in bodily function, especially apnea, which are thought to result from interference with the oxygen supply. In both of these approaches, anoxia is clearly conceived to be a state within the organism or a response of the organism to environmental deficit. A third approach defines anoxia in terms of the mechanism of interference with the oxygen supply. In animal research, the experimenter provides this interference by reducing oxygen in an air chamber, clamping the umbilical cord, etc. The response of the organism to the interference is by no means overlooked, however. Either on the basis of previous experience or present trial and error, the experimenter adjusts the time of exposure or the oxygen content of the air to a point just short of a too great mortality rate. In brief, he uses the criterion of some immediate disturbance in bodily function to determine whether the mechanism of interference with oxygen supply has, in fact, produced an "inadequate" supply. He then tests for effects on later development.

In our concern with this question of how best to define early anoxia, we were interested initially in using a measure of blood oxygen content. This is a relatively new technique, and so far only two research groups[25, 27] have undertaken longitudinal investigations employing it. One of these has already reported that no relationship was found between oxygen levels at birth and later intelligence levels.[25] Our own investigations, although based entirely on neonatal data, have led us to question whether any relationship with later development can be expected.

These results have already been reported in detail and need be summarized only briefly. In line with other studies, we found that complications of delivery and, to a lesser extent, the use of anesthesia, lowered the cord oxygen and that these effects diminished rapidly throughout the first hour. Interestingly enough, we found that fetal complications were *not* reflected in lower cord values, although such infants were less likely to have achieved normal oxygenation by one hour after delivery and their clinical

condition was more likely to be unsatisfactory.[28] Carrying this further, we attempted to relate oxygen levels to the infants' clinical status. We found only a slight relationship when the seriousness of the immediate clinical condition was rated by considering muscle tone, cry and respiratory delay, methods of resuscitation, etc., and no relationship between oxygen level and behavior tests given twenty-four hours later.[26] We concluded that, while blood oxygen saturation is obviously valid as a measure of the blood oxygenation at the moment, it changes too rapidly, probably in response to many factors, to be of practical assistance in long-term prediction. Since cord and ten-minute values, for example, did not correlate highly with the blood oxygen status at one hour, it is not surprising that the saturation of oxygen in the blood at one moment in time should fail to show any significant relationship to more prolonged states.

If, then, the precise physiological measure does not provide the kind of information in which we are interested, what alternatives are available? As noted above, the most common definition has been in terms of a "clinical" disturbance in bodily function. Direct interference with the oxygen supply of the human infant has not, of course, been attempted, but a number of studies have defined anoxic groups in terms of conditions which are thought to be the mechanisms of interference, such as prolonged labor, difficult deliveries, and maternal illnesses during pregnancy. Some studies have used only one or the other of these definitions; in others, they have been combined.

Observations recorded in the medical chart have usually provided the basic data. This procedure can be and has been criticized for lacking objectivity, standardization, and reliability. It is possible, however, to develop reasonably reliable and objective methods of rating the information recorded in a medical chart, provided the hospital uses a standard record form.[29] Better methods of making clinical observations are also possible. Apgar[30] has provided an excellent scale for rating the immediate natal condition of the infant, although she has not yet reported relationships between these ratings and later development.

We felt, however, that measuring the condition of the infant immediately after birth would not necessarily identify those infants whose response to anoxia was most severe, as judged by the fact that symptoms persisted for several days. It seemed reasonable to expect that an infant who remained apathetic and flaccid for forty-eight hours would be more likely to show later sequelae than an infant who responded quickly to therapy, even though the condition of both immediately after birth was judged to be essentially similar. In order to take into account any disturbance in functioning over a longer period of time, we employed three techniques. First, pediatricians made ratings of the medical history during the hospital stay in terms of whether the prognosis appeared good, questionable, or guarded. Second, from factors in the medical chart a weighted "prognostic score" was obtained. Third, five behavioral tests were devised.[29] The three measures were closely related and we, therefore, felt justified in using the more objective and refined

test procedures as a measure of clinical condition.

In establishing meaningful criteria of early anoxia, one must decide whether it is necessary or desirable to consider as anoxic those infants who were exposed to mechanisms which may have interfered with fetal oxygen supply. Potter and Adair,[31] for example, feel that "primary anoxia is always intrauterine in origin," and list a number of conditions which can lead to it. Pediatricians also, in evaluating the prognosis of an individual child, are concerned with whether or not there may have been fetal anoxia. The possibility of fetal anoxia is usually considered when (a) there are signs that bodily disturbance, such as changes in the fetal heart rate or meconium in the amniotic fluid, occurred prior to birth and (b) there is evidence that possible mechanisms of interference with the oxygen supply were present, such as a prolapsed cord, maternal toxemia, etc. But whether these data are of much value as indicators of fetal anoxia is far from settled. If they are not, it would be preferable to ignore them in selecting anoxic subjects, as has been done in most of the prospective studies. If they are, then studies must in some way control for their effects. We had some evidence bearing upon this point in unpublished data from other studies. As the results seemed relevant to this question of determining criteria of early impairment, it is worth while to present them at this point.

INFLUENCE OF FETAL FACTORS

In an earlier study,[29] the purpose of which was to establish the relationship among our three measures of clinical condition, we found that the average score of a mixed group of sixty anoxic infants on the Newborn Behavior Tests was lower than that of a normal group. The variability among infants was large, however, and many "anoxic" infants showed behavior that could not be differentiated from normal. The question we would now like to ask is: Did the presence of fetal designs or complications in this group increase the likelihood of lowered performance on the Behavior Tests?

With the same data it is possible to inquire simultaneously whether complications of delivery, alone or in combination with postnatal anoxia, increased the likelihood of impaired test performance. It is well known that difficult deliveries can produce damage, but for this analysis cases with clear signs of mechanical trauma, such as skull fracture, were not studied. Interest was rather in injuries which, if they occurred, would be minimal and would presumably be due to anoxia arising indirectly from events at birth. This second question was posed as follows: In the absence of observable signs of mechanical injury, prenatal or postnatal anoxia, will a complicated delivery alone impair behavioral performance? With compounding of these complications, will impairment be relatively greater?

Procedure.—

Subjects: For this analysis, 131 full-term infants born on the inpatient service of the St. Louis Maternity Hospital between July, 1953, and December, 1955, were used. Of these, sixty-one were considered "anoxic," eight had no complication other than a difficult delivery, and sixty-two had no

complications. Methods of selecting subjects have been described in detail in previous publications.[29, 32, 33] It will suffice here to mention that we attempted to examine all infants experiencing postnatal anoxia.

Behavior Tests for the Newborn: These tests[32, 33] were administered to subjects within twenty-four hours after birth if possible, or as soon as the condition of the infant permitted. A correction was made for differences in the performance due to race and age at the time of testing.[33] The differential effect on test performance of the three kinds of complications (fetal, delivery, and postnatal) was determined by means of a three-way analysis of variance. A general description of the criteria used in determining whether a complication was present or absent has already been given in greater detail.[29] The experimental design and number of subjects in each of the eight groups are shown in Table I. It will be noticed that this design allows simultaneous determination of the effects of three variables by comparing performances where there are no complications, when each of the complications is present alone, for every possible combination of two complications, and for all three complications present together.

Results.—In Table II, the mean Behavior Test scores of the eight groups are arranged in rank order. These are standard scores, representing a distribution having a mean of 50 and a standard deviation of 10. Values below 50 indicate poorer performance. It will be noticed that scores decrease as number of complications increases. The decrease is least when complications of delivery are present either singly or in combination. Impairment is greater after postnatal anoxia and greatest of all when there are fetal complications.

The significance of these effects was tested statistically, with results shown in Table III. The weighted mean differences appearing in Table III are the differences between the four groups in which a particular complication, such as difficult delivery, was present and the four groups in which it was absent. Because some groups had many subjects and some few, each mean difference was weighted for the number of cases which had contributed to it. Snedecor's[34] method of correct-

TABLE I. NUMBERS OF SUBJECTS IN EACH GROUP

COMPLICATION	PRENATAL, ABSENT		PRENATAL, PRESENT	
	DELIVERY, ABSENT	DELIVERY, PRESENT	DELIVERY, ABSENT	DELIVERY, PRESENT
Postnatal, absent	62	8	16	7
Postnatal, present	7	5	19	7

TABLE II. MEAN BEHAVIOR TEST SCORES ARRANGED IN DECREASING ORDER

	COMPLICATIONS						
	NONE	ONE			TWO			THREE
		DELIVERY	POST	PRE	DELIVERY POST	DELIVERY PRE	POST PRE	DELIVERY POST PRE
N	62	8	16	7	5	7	19	7
X	48	46	45	44	41	39	35	35

ing for disproportionate numbers was used. Groups *with* complications were poorer than groups *without*, the difference ranging from an impairment, on the average, of only 2.45 Behavior Score points with delivery complications to 7.03 score points with prenatal complications.

Are such differences significant, or could they have arisen as a result of chance variability? The statistical test allows us to remove the effect due to the other two variables when we wish to determine the effect of a single variable. It also permits a statement of the probability that the effect is a chance fluctuation. As shown in Table III, a difference as large as the one between complicated and uncomplicated delivery groups might occur by chance somewhat more often than five times in a hundred. Since a probability of not more than five times in one hundred is the usual criterion for significance of results, we would have to conclude that a significant effect of delivery complications does not appear in our groups. A difference as large as that between groups with and without postnatal anoxia, however, would be expected by chance less than one time in one hundred. Prenatal complications also have a statistically significant effect.

None of the interactions approaches significance. This means that a combination of complicating factors does not result in any greater impairment than would be expected from adding the effects of the individual complications.

To summarize, a difficult delivery in the absence of mechanical injury did not have a significant differential effect on the test performance. When fetal complications were present, however, the effect on performance was as great as or greater than the effect of a period of immediate postnatal anoxia

TABLE III. ANALYSIS OF VARIANCE DUE TO THREE MAIN SOURCES AND THEIR INTERACTIONS

	VARIABLE			INTERACTION			
	DELIVERY	POST	PRE	DELIVERY X POST	DELIVERY X PRE	POST X PRE	DELIVERY POST PRE
Weighted differences	2.45	4.35	7.03				
F	2.07	8.18	18.89	.44	1.73	.87	.81
P	>.05	<.01	<.01		Not significant		

DISCUSSION

This evidence suggests that maternal complications during pregnancy and labor and signs of fetal distress may be valid indicators of intrauterine anoxia. Infants with these complications were impaired in their performance on Behavior Tests, with the relative impairment as great as or greater than that following a period of immediate postnatal anoxia. It is not surprising that reduction of the oxygen supply during fetal life should be deleterious to the infant, since longer and perhaps more profound periods of anoxia can occur undetected without the possibility of any therapy. The question of practical interest is whether we can have any accurate knowledge of a dangerous reduction of the intrauterine oxygen. The present studies suggest that clinical signs of it warrant concern as much as a period of temporary anoxia after

birth. It would appear worth while to pursue this question further and establish which fetal complications and signs are of greatest significance. Because our attention was originally directed to postnatal anoxia, we did not seek cases with fetal complications that had not also had postbirth difficulty. Thus, these cases were obtained only indirectly. An increase in the number of such cases would be desirable for all future studies.

In our sample, performance was somewhat impaired following complications of delivery. Although this effect was not statistically reliable, it might be demonstrated by increasing the number of cases studied. The significance of this finding lies in a comparison with the impairment when either postnatal or prenatal anoxia was present. In considering an infant's total perinatal history, knowledge that the delivery was difficult (but without signs of mechanical injury) adds relatively little to our ability to be able to predict behavioral status. It is probable that some of our infants suffered a period of postnatal anoxia as a direct result of difficulties during delivery, but the effects of anoxia under these circumstances were not significantly greater than under circumstances where the cause of anoxia could not be identified. This is in line with the finding of Lilienfeld and co-workers[2, p. 639] that difficulties "which are more prone to produce fetal anoxia" were more common in several defective groups than were "mechanical difficulties of delivery."

The emphasis in this discussion has been on factors leading to impairment. However, it is equally important to point out that a large number of infants for whom concern might be felt did not, in fact, show any impairment. As far as their behavior was concerned, they appeared to be completely normal by the time of testing. Thus we are still faced with the challenge of identifying those protective factors which insulate certain infants during ordinarily injurious experiences, or, conversely, of establishing what it is that lowers the threshold of resistance. This point was dealth with at greater length in an earlier paper[29] where figures were presented showing the range and overlap between normal and anoxic groups.

In this and previous studies we have dealt only with the neonate, but the findings have implications for research which attempts to assess the later consequences of perinatal experiences. We are more concerned with lasting than with transitory effects and must eventually judge these early experiences by their effect on behavior when the child has become somewhat older. In attempting to explain the failure of several recent studies to discover any consequences of natal anoxia, we pointed out four design factors which must be considered in evaluating conclusions. These were: approach to the problem (prospective or retrospective), measures of later impairment, equating of control and experimental groups, and the definition of early anoxia. It is this last factor with which we have been concerned in our neonatal studies and, on the basis of these, it seems possible to offer specific suggestions.

First, while there can be no scientific objection to defining anoxia in terms of a physiological measure, such as blood oxygen saturation, such a measure appears to reflect very transitory levels of oxygenation. Since it is not necessarily closely related to even the immediate neonatal condition,

it should not be surprising to find it unrelated to more remote events. It seems necessary, therefore, to fall back on a less exact but more meaningful clinical criterion.

Second, even though a clinical criterion is used, it should permit some ordering as to degree and should be as objective and reliable as possible. Even gross ordering in terms of severity would be desirable if it permitted the identification and separation of the more severe cases from those who might not be expected to suffer detectable effects. Identification of the most serious cases, whether by rating the immediate clinical condition of the infant or by measuring condition during the neonatal period, or by combining both measures, is important in improving the sensitivity of research designed to study later effects. Since mildly anoxic cases far outnumber the more serious cases, they may serve only to dilute or obscure a significant effect. We have already emphasized the point that only a relatively small per cent of an "anoxic" group can be expected to show gross effects. With care, objectivity and quantification can be obtained by weighting factors in the medical chart. Apgar's[30] method of evaluating the infant's condition immediately after birth and our[29] own prognostic score seem to accomplish this.

A third factor which needs to be considered is the rapidity of recovery during the neonatal period. There are, after all, two aspects to any trauma—the severity of the trauma itself and the response of the organism to it. Many lines of evidence have shown that the two are not always perfectly correlated. Some infants may be very apneic at birth but appear pink and robust within the hour. Others may have secondary apnea, or may continue to be sluggish and apathetic for several days following birth. Administration of the Behavior Tests at twenty-four to forty-eight hours after birth is one way of taking into consideration the recovery factor.

A final, and perhaps more crucial, question is the h a n d l i n g of fetal anoxia. Our results suggest that signs of fetal distress and complications during pregnancy are as serious as if not more serious than a temporary period of postnatal anoxia with respect to impairment of neonatal behavior patterns. In attempting to determine the effects of early anoxia, then, it would certainly seem desirable to include cases with fetal anoxia. Most of the retrospective studies starting from groups with known defects have included fetal complications. On the other hand, studies beginning with the neonate have generally investigated only the effects of postnatal anoxia. This may be one factor which helps to account for the discrepant conclusions obtained in the two types of studies. There can be no objection to limiting the area of concern to postnatal anoxia so long as care is taken that the results are not contaminated by the effects of fetal anoxia. None of the studies seems to have been concerned with this possibility. Neither the equating of control and experimental groups for the possibility of fetal anoxia nor the exclusion of such cases from both groups has been discussed.

We do not wish to underestimate the difficulties that plague research in this area or to imply that results are always meaningless if the investigators have been unable to use the most desirable technique. Certain conclusions tentatively emerge despite the differences in method and limitations of

method. The extreme statement that early anoxia is either lethal or leaves *no* residual effects is probably not a tenable position. Evidence that the infant is more resistant to oxygen deprivation than the adult suggests that a greater deprivation will be necessary to produce any effects. It does not imply that the adult organism may have degrees of response to deprivation while the infant can respond only in an all-or-none fashion. The question is rather whether any *significant* effects occur and what is meant by significant. On the whole, studies of defective groups suggest a relationship between early anoxia and later defects. That this association is purely a by-product of congenital maldevelopment seems less likely in view of animal studies. Any speculation as to the size of the relationship would be premature, although it seems safe to state that the majority of infants exposed to *mild* degrees of postnatal anoxia will not show *gross* central nervous system or mental impairment. It is not possible to make any conclusions about milder degrees of impairment, but these may be more frequent than is currently realized.[2, 11, 14, 21] Detection of them will in large measure await the development of instruments which are sensitive to the kinds of impairment most likely to occur.

SUMMARY

In this paper we have reviewed major findings from several studies designed to test the hypothesis that anoxia is a significant perinatal experience. Several design factors which may help to account for the discordant conclusions arrived at by various investigators were pointed out. These were: approach to the problem (prospective or retrospective), criteria of later impairment, use of control groups, and criterion of early anoxia.

It is the factor of definition of early anoxia with which we have been especially concerned in this and earlier studies of neonates. On the basis of these studies, several conclusions and suggestions emerged. First, blood oxygen saturation appears to reflect very transitory levels of oxygenation. Since it is not necessarily closely related to even the immediate neonatal condition, it would not be surprising if there were no relationship with more remote events. It seems necessary, consequently, to employ a less exact but more meaningful clinical criterion of anoxia. Second, even though a clinical criterion is used, it should permit some ordering as to degree in addition to satisfying the usual scientific demands for objectivity and reliability. Third, there is considerable variability in the postnatal rate of recovery of anoxic infants. Measurement of these differences provides a way of identifying those infants who may be most likely to show residual effects. Fourth, events believed to lead to fetal anoxia were associated, in our subjects, with relatively greater impairment in performance on Newborn Behavior Tests than either postnatal anoxia or nonmechanical delivery complications. This finding highlights the necessity of controlling for fetal factors in any research designed to assay the effects of anoxia.

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RECURRENT STAPHYLOCOCCUS AUREUS PNEUMONIA AND EMPYEMA TREATED WITH NOVOBIOCIN

Review of the Literature, With Report of a Case

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THE problem of *Staphylococcus aureus* infection in infancy is a frequent one, often serious, and far from solved by the antibiotics in our present therapeutic armamentarium. The reason for the relative failure of antibiotics against this organism is that in the past few years the *Staph. aureus* hemolyticus has developed increasing resistance to penicillin and many other antibiotics in current use. The purpose of this paper is to report the good response to a new antibiotic, novobiocin (Cathomycin*), of a recurrent *Staph. aureus* pleuropneumonic infection, which had not properly responded to other current antibiotics. At the present writing there seems to be no report in the pediatric literature of the successful use of this drug in the treatment of staphylococcus pneumonia in infancy.

Cathomycin is produced by fermentation from an actinomycete, *Streptomyces spheroides.*[1] Although it is active against many gram-positive and some gram-negative organisms, it is especially effective against staphylococci and many strains of the proteus group, including those strains resistant to most antibiotics.[2-4] In vivo studies disclose that there is apparently no cross-resistance between novobiocin and the other antibiotics in general use.[5] It is absorbed rapidly from the gastrointestinal tract and detectable levels are found in the serum more than twelve hours after administration.[5-7] Novobiocin is freely distributed in the various body fluids, except the cerebrospinal fluid.[6, 7, 9] Elimination from the body is slow, but available evidence does not reveal accumulation in the serum of the patients receiving the drug for extended periods.[6, 9, 12]

Lubash and co-workers[8] tested a total of 182 strains of *Staph. aureus* in a laboratory investigation of novobiocin. Only one strain failed to be inhibited by 1.0 meg. per milliliter of novobiocin, and many were inhibited by much lower concentrations of the antibiotic. The majority of these strains were resistant to one or more of the other drugs tested, namely, penicillin, streptomycin, tetracycline, erythromycin, and chloramphenicol. They also tested the absorption and distribution of novobiocin by administering orally to a group of men single doses of 0.5 Gm. The peak concentrations in the serum were usually reached before two hours and varied from 6.4 to 51.2 meg. per milliliter at the end of the second hour. In six

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*The trade name of Merck Sharp & Dohme for novobiocin.

hours the levels were still high, ranging between 6.4 and 12.8 meg. per milliliter. In one patient absorption was delayed to the extent that no measurable drug was found in the first two hours. However, at the end of the fourth hour the serum concentration of novobiocin was 12.8 meg. per milliliter and remained at this level after six hours.

Lin and Corriell[9] tested the sensitivities of twenty-two strains of *Micrococcus pyogenes* var. *aureus* isolated from patients in three different hospitals. Most of these patients had been treated with antibiotics without clinical improvement. Of these strains, nineteen were resistant to penicillin, twelve to chloramphenicol, and five to erythromycin. All strains were sensitive to novobiocin, the minimal inhibitory concentration being less than 1.6 meg. per milliliter except for one which was sensitive to 6.25 meg. per milliliter. To collect data on dosage level, they administered novobiocin to a group of seventeen patients. They found much higher serum levels than were obtained by any other antibiotic in comparable dosage. These higher levels persisted in good concentration for eight hours or more.

The most common side reactions of novobiocin have been allergic rashes.[6, 8, 9, 11, 12] These have included pruritic maculopapular eruptions, morbilliform, petechial, papulovesicular rashes, and exfoliative dermatitis. Other untoward effects have been gastrointestinal upsets, such as nausea, vomiting, and diarrhea, and transient leukopenia.[6, 9, 10, 11] In a small percentage of patients, yellowish discoloration of the scleras has been noted. Available evidence indicates that this is due to a metabolite of the drug and not bile pigment.[11] Liver function tests in these cases have been normal. The drug is bound extensively by serum proteins but the novobiocin complex is readily dissociated in vivo.[7] No moniliasis, a frequent sequel of other antibiotics, has been reported thus far.

Limson and Romansky[13] found novobiocin effective in the treatment of thirty patients with bacterial pneumonia (pneumococcal and nonpneumococcal). Side reactions were few and disappeared within forty-eight hours after stopping the drug. Martin and associates,[6] summarizing their clinical experience with novobiocin in thirty-four cases, reported the recovery of a patient who had pneumonia and pleural effusion due to *Diplococcus pneumoniae*. In a group of patients with staphylococcal infections treated with novobiocin by Lin and Corriell,[9] there were three patients with pneumonia from whose throats staphylococci were cultured. Two recovered and the one fatal case was secondary to fibrocystic disease of the pancreas. This patient had been treated previously with penicillin, streptomycin, and chloramphenicol, and cultures grew *Pseudomonas aeruginosa*, as well as staphylococci.

CASE REPORT

First admission: B. C., a 3-week-old white male infant, was admitted on May 3, 1956, with a two-day history of fever, cough, and respiratory difficulty. He had been entirely well up until that time, thriving since leaving the hospital a week after birth.

Positive findings at the time of admission revealed some nasal discharge and a moderately reddened throat. Medium and fine râles were heard at the left base but there was no dullness to percussion or change in breath sounds. The temperature was 100.2° F. A diagnosis of bronchopneumonia of the left lower lobe was made and

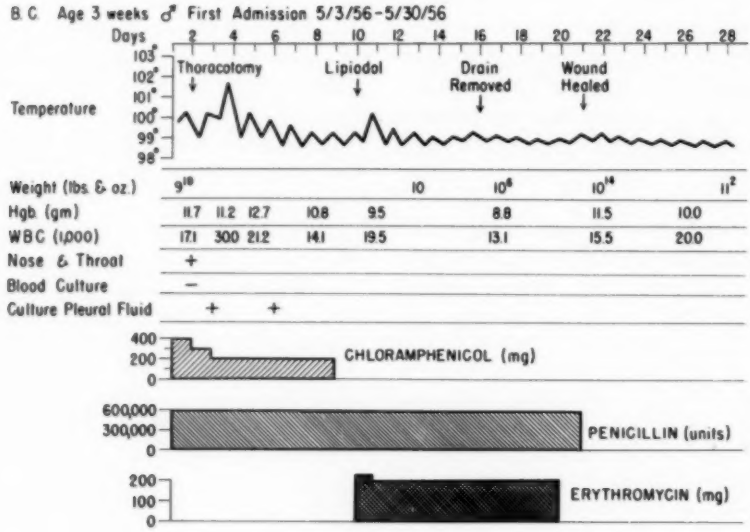
B. C. Age 3 weeks ♂ First Admission 5/3/56-5/30/56
Days
Temperature
Thoracotomy
Lipiodol
Drain Removed
Wound Healed
Weight (lbs. & oz.)
Hgb. (gm)
WBC (1,000)
Nose & Throat
Blood Culture
Culture Pleural Fluid
CHLORAMPHENICOL (mg)
PENICILLIN (units)
ERYTHROMYCIN (mg)

Fig. 1.

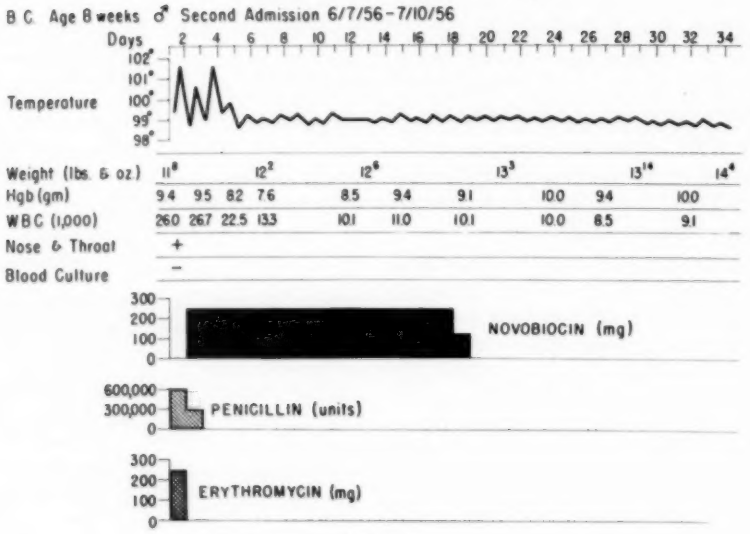
B. C. Age 8 weeks ♂ Second Admission 6/7/56-7/10/56
Days
Temperature
Weight (lbs. & oz.)
Hgb (gm)
WBC (1,000)
Nose & Throat
Blood Culture
NOVOBIOCIN (mg)
PENICILLIN (units)
ERYTHROMYCIN (mg)

Fig. 2.

nose and throat cultures were taken. The infant was placed in an oxygen tent. Crysticillin, 600,000 units daily was administered. In addition, chloramphenicol was given intramuscularly, 200 mg. every twelve hours for the first day, 150 mg. every twelve hours for the second day, and thereafter 100 mg. every twelve hours. An x-ray several hours after admission showed an infiltration in the lower portion of the left lung corroborating the clinical diagnosis of pneumonia.

On the next day, the baby was found to be in extreme respiratory distress. Respirations were very rapid, shallow, and labored. His color was cyanotic and suprasternal and infrasternal retractions were present. Heart sounds were rapid and weak and heard best on the right side of the chest. Breath sounds were absent on the left side with dullness rather than hyperresonance elicited on percussion. No râles were heard. X-ray disclosed the presence of a massive pneumothorax on the left side with almost complete atelectasis of the left lung. The heart, trachea, and mediastinum were shifted to the right with compression of the right lung.

A needle was inserted into the left chest, releasing a large amount of air under tension, and an intercostal drainage under water was set up. Approximately 8 c.c. of pus was removed from the pleural cavity. Culture of the pus from the chest, as well as the nose and throat cultures, was positive for *Staph. aureus* hemolyticus. Sensitivity studies showed the organism to be resistant to penicillin, moderately sensitive to erythromycin, and sensitive to Chloromycetin. Blood cultures were negative.

Hemoglobin on the day of admission was 11.7 grams and the hematocrit was 37 per cent. The white blood count was 17.150 with 47 per cent polymorphonuclears, 1 per cent myelocytes, 41 per cent lymphocytes, 3 per cent basophils, and 8 per cent eosinophils. On the next day his white blood count rose to 30,050 with 56 per cent polymorphonuclears, 1 per cent staffs, 10 per cent monocytes, and 33 per cent lymphocytes.

After underwater intercostal drainage was begun, the baby became comfortable and his color returned to normal. He ran a low-grade fever up to 101.6° F. for a few days and then became afebrile for the remainder of his hospital stay. Serial x-ray films revealed diminution and absorption of the pneumothorax with gradual subsidence of the pneumonia and empyema. Radiolucent areas appeared in the lateral portion of the left chest. At first it was difficult to determine whether these areas were in the lung, representing a pneumatocele, or in the pleural cavity, representing loculated air collections. A small amount of Lipiodol was injected into the drainage tube but the sinus tract to the lung could not be determined. However, successive films during the course of the next few weeks definitely disclosed the lesion to be a pneumatocele which was gradually diminishing in size. At the time of discharge there were still a pleural reaction and a small amount of Lipiodol noted.

The drainage tube which had been inserted on the day after admission was removed fifteen days later. Shortly thereafter the chest wound healed. The baby appeared very well, was afebrile, and was feeding and gaining weight.

Despite the in vitro resistance of the cultured staphylococci to penicillin, this drug was given in large doses (600,000 units daily) for almost three weeks. In addition, chloramphenicol was given intramuscularly in dosage of 50 mg. per kilogram daily for ten days and then erythromycin was given in similar dosage orally for the next ten days. Condition on discharge May 30, 1956, appeared good.

The discharge diagnosis was staphylococcal pneumonia of the left lower lobe, pyopneumothorax, and pneumatocele (left lower lobe).

Second admission: The baby was apparently well for almost a week after discharge from the hospital and

Fig. 3.—Admission x-ray of chest, disclosing an infiltration in the lower portion of the left lung. The right lung and the heart appear normal.

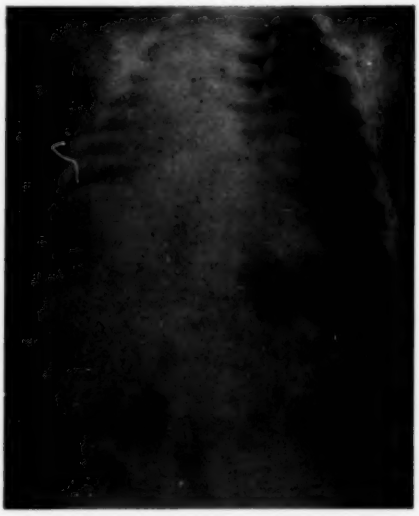

Fig. 4.—The presence of a pneumothorax on the left side with almost complete atelectasis of the left lung. The heart, trachea, and mediastinum are markedly shifted to the right side with compression of the right lung and decreased aeration of the upper portion. Some increase in markings is seen in the right lung. This is due to compression rather than an active infiltration.

Fig. 5.—Shows Lipiodol to enter a small sinus tract just distal to the end of the tube. The exact location of this sinus tract is not determined with certainty. The Lipiodol does not appear to flow into the pleural space.

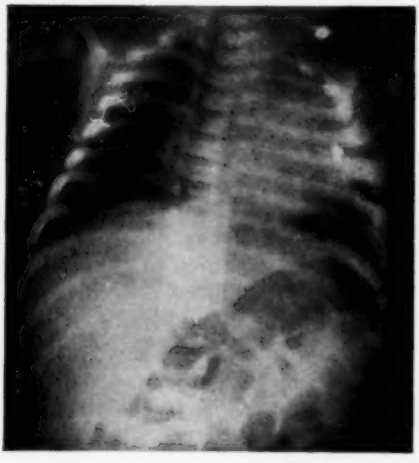

Fig. 6.—There are radiolucent loculations in the lower portion of the left chest. The appearance is very suggestive of emphysematous bullae (pneumatocele) in the lung.

then began to have fever again accompanied by rapid, labored respirations and a high-pitched cry. Examination upon readmission June 7, 1956, revealed an irritable, sick baby in respiratory distress. Positive findings were marked dullness to flatness on percussion in the left anterior chest, left axilla, and upper left posterior chest with some hyperresonance in the left lower chest. Breath sounds were diminished and no râles were heard.

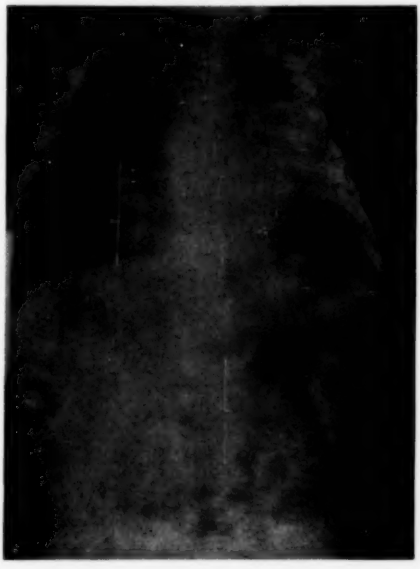

Fig. 7.—There is a pleural density in the upper half of the left chest. A small amount of Lipiodol is still present. There appears to be a slight shift of the mediastinum to the left side, suggesting an element of atelectasis in the left upper lung.

A diagnosis of recurrent staphylococcal pneumonia of the left upper lobe and empyema was made. The temperature was 101.4° F. and respirations 64 per minute. The white blood count was 26,000 with 58 per cent polymorphonuclears, 37 per cent lymphocytes, and 5 per cent monocytes. The hematocrit was 30 per cent. Nose and throat cultures were positive again for *Staph. aureus*. Repeat blood cultures were negative.

The infant was placed in an oxygen tent. Penicillin, 600,000 units daily, and intramuscular erythromycin, 50 mg. per kilogram daily were discontinued within forty-eight hours because of severe induration and redness of the buttocks. The baby appeared desperately sick and his respiration had risen to 80 per minute. Abdominal distention was pronounced. X-ray disclosed a pleural density in the upper half of the left chest. A small amount of residual Lipiodol was seen below this region. There appeared to be a slight shift of the mediastinum to the left, suggesting an element of atelectasis in the left upper lung. The lower lung still revealed the radiolucent areas described in the previous admission.

Novobiocin was started orally in dosage of 50 mg. per kilogram daily. This was given in four divided doses every six hours and mixed with fruit or formula. The medication was given for a total of nineteen days and tolerated well. There were no gastrointestinal reactions, such as nausea, vomiting, and diarrhea, and no skin eruptions.

Within forty-eight hours after first administration of the drug, he became afebrile and remained so for the duration of his hospital stay. His respirations became normal and he appeared vastly improved. Oxygen was discontinued in several days. The white blood count, which had risen to 26,700 by the time the antibiotic was started, fell to 13,350 several days later and gradually became normal over a period of several weeks. His white blood count at the time of discharge was 9,150 with 19 per cent polymorphonuclears, 70 per cent lymphocytes, 5 per cent monocytes, and 6 per cent eosinophils.

Serial x-rays disclosed gradually increasing aeration of the upper portion of the left lung and gradual subsidence of the pneumonic process. The homogeneous density obscuring the upper half of the left chest, which on lateral views was located in the anterior portion, was reported as pleural reaction and partly thymus. The lower

portion of the left lung appeared well aerated and the pneumatocele was decreasing in size.

The baby was clinically well at the time of discharge and was eating eagerly and gaining weight. His blood count was normal. The roentgen films still showed some density in the upper half of the left chest, which was interpreted as pleural reaction. The lower lobe which was the site of the original insult was reported as normal.

Fig. 8.—Some density is still noted in the upper half of the left chest. This is probably due to pleural reaction. The trachea does not appear to be displaced. The left lower lobe and the right lung appear normal.

Since his discharge from the hospital he has continued to thrive exceedingly well. His weight at 4½ months was 17 pounds and the parents state that he has been playful, comfortable, and alert. Follow-up x-rays at monthly intervals have shown gradual subsidence of the pleural thickening.

DISCUSSION

The past two decades have witnessed a continuous change in the medical treatment of *Staph. aureus* pneumonia and empyema in infants, accompanied by a decrease in the mortality rate. This period has also seen the virtual disappearance of the septic type of staphylococcal pneumonia and empyema secondary to generalized staphylococcal sepsis.

In describing primary bronchogenic staphylococcal pneumonia in 1938, Cohen[14] stated that the mortality rate of staphylococcus empyema in infants was between 50 and 100 per cent, probably near the latter figure in very

Fig. 9.—Infant at 5 months of age. He is in excellent health, alert, and vigorous.

young infants. Medical therapy at that time consisted of staphylococcus antitoxin and supportive measures.

Forbes[17] reviewed forty-two cases of acute staphylococcal empyema seen at the St. Louis Children's Hospital over a ten-year period, from 1934 to 1943, inclusive. The mortality rate for this series was 26.2 per cent. Of the thirty-four patients in this series who were given one of the sulfonamide drugs, only four were definitely benefited by the use of chemotherapy. The author emphasizes the importance of pyopneumonthorax complicating staphylococcal empyema.

In 1944, McBryde[20] reported the first two cases of *Staph. aureus* pneumonia treated with penicillin. Both infants, 4 and 5 weeks of age, respectively, were not responding to sulfadiazine, but dramatic improvement occurred after penicillin was started. It is interesting to note that the total amount of penicillin given the infants was 41,000 units in one case and 50,000 units in the other—how different from today!

For the next decade penicillin was quite effective in the treatment of staphylococcal infections of the lung and pleura[21] but resistance to this antibiotic developed steadily, necessitating another drug of choice. In 1952, Feldman and Annunziata[22] reported an outbreak of *Staph. aureus* infections in a newborn nursery. Among the various conditions caused by this organism were four cases of *Staph. aureus* pneumonia complicated by lung abscess. Two of the infants recovered and two died, despite therapy with Aureomycin and streptomycin.

In 1953 Kanof and associates[23] reported a series of forty-one infants and children with staphylococcal pneumonia treated with sulfonamides, with sulfonamides plus penicillin, and with Aureomycin plus penicillin. With sulfonamide treatment alone, the mortality rate was 50 per cent, with sulfonamides plus penicillin 25 per cent, and in twelve cases treated with Aureomycin plus penicillin there were no deaths. They made the interesting observation that with the advent of newer antibiotics empyema is less common and frequently clears up without paracentesis, without which there is no opportunity for obtaining a culture of the fluid. Hence, the diagnosis of staphylococcal pneumonia and empyema must depend more on typical clinical criteria and x-ray findings, which they describe.

Within the past few years, infections caused by staphylococci which have become resistant to Aureomycin (chlortetracycline) have frequently shown cross resistance to tetracycline and oxytetracycline, so that at present erythromycin and chloramphenicol are often the antibiotics of choice when the *Staph. aureus* is involved. Since these latter drugs are now being used with increasing frequency, the usual pattern of emerging resistance is becoming more manifest here again. Thus the search for a new drug to be used where others fail is a never-ending one.

Novobiocin was given in adequate doses, namely, 50 mg. per kilogram per twenty-four hours. This was administered in a powder mixed with formula or strained fruit, every six hours. Despite the fact that the antibiotic was given continuously for almost three weeks, there were no side effects or toxic manifestations of any kind. As mentioned earlier, the baby presented a marked improvement within forty-eight hours after the first administration of the medication. The temperature subsided, respirations became normal, and he no longer appeared sick. Accompanying this was a decline in his leukocytosis to normal levels. Although the baby has thrived very well since discharge from the hospital and appears in excellent health, there still remains some pleural density in the left upper chest. This is apparently a residual thickening of the pleura and has been receding.

SUMMARY

A case of recurrent *Staph. aureus* hemolyticus pneumonia and empyema treated with novobiocin (Cathomycin)

has been described. The recurrence followed the use of penicillin, Chloromycetin, and erythromycin. To our knowledge, this is the first report in the pediatric literature of this disease in early infancy treated with this antibiotic.

Novobiocin was administered in a dosage of 50 mg. per kilogram daily. It was given as a powder every six hours, mixed with formula or fruit. Despite the continuous administration of the drug in adequate dosage for nineteen days, there were no side effects or toxic manifestations of any sort.

Since the staphylococcus has acquired increasing resistance not only to penicillin but to other antibiotics as well, the search for newer and more potent drugs against this ubiquitous and ever-dangerous organism must be unceasing.

I am indebted to Dr. Philip Cohen for his aid in the preparation of this paper.

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SERIOUS REACTIONS TO NOVOBIOCIN

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FOR approximately the past year, novobiocin has been available for clinical trials. It has recently been released for general use with the recommendation that it has a definite place in antibiotic therapy and is particularly effective for gram-positive infections. It has been recognized by all investigators that there is an appreciable incidence of allergic manifestations appearing during the use of this drug. Welch and associates[12] have recently reported on an investigation into the sensitizing potential of this drug. It was their opinion, upon reviewing the literature concerned with clinical trials, that these reactions were directly proportional to dosage and duration of therapy. Most reactions in adults have occurred on dosage levels approximating 2 Gm. per day and on about the sixth day of treatment or later. In a controlled study using what he considered to be an effective level of dosage, but which was much less than previously used by most investigators, they were able to attribute only one reaction to novobiocin in a treatment group of 208. There was, however, a definitely increased incidence of gastrointestinal manifestations when compared with the two control group (one penicillin and the other a placebo group). In the treatment groups reported so far by various authors[3-11] there has been a varying incidence of reactions. The most noteworthy among these have been the apparent allergic reactions manifested by urticaria, generalized erythema, or maculopapular eruptions. On occasion, serum sickness has been noted. Most of these reactions have also been accompanied by fever. These reactions have almost all been unequivocally attributed to novobiocin, and with one exception it has been thought necessary to discontinue the drug. In this one exception the drug was continued without apparent detriment for an additional four days.[6] The incidence and nature of the reported complications attributed to novobiocin have been summarized in Table I. The over-all incidence in these collected cases has been 12.7 per cent. The great majority of these patients had been receiving novobiocin orally in doses ranging from 2 to 4 Gm. per day for several days at the time of appearance of the sensitivity reaction. Therapeutic dosage has been considered to lie within safe limits at 15 to 60 mg. per kilogram per day.[2] In general, 2 Gm. per day has been the usual dose employed by

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most investigators. Since little concerning untoward reactions in children has been reported and since our own limited clinical experience with this new antibiotic appears to indicate that serious reactions occur with surprising frequency in children given this drug, we feel that it is important to report the various reactions we have encountered.

TABLE I. TOXIC REACTIONS TO NOVOBIOCIN

AUTHOR	PATIENTS TREATED	REACTIONS	MANIFESTATIONS
Martin et al.[3]	34	6	Angioneurotic edema, papular eruptions, urticaria, serum sickness
Lin and Coriell[4]	16	1	Urticaria
Mullins and Wilson[8]	30	0	—
David and Burgner[9]	29	11	Maculopapular eruptions, increased indirect bilirubin
McHardy et al.[10]	21	7	Petechial erythematous rash, morbilliform rash, nausea and vomiting
Nichols and Finland[11]	52	5	Erythematous or maculopapular eruptions, fever
Limson and Romansky[5]	30	2	Urticaria
Morton et al.[6]	41	2	Urticaria
Milberg et al.[7]	55	5	Maculopapular eruption, pruritus, fever
	308	39	Incidence—12.7%

CASE REPORTS

CASE 1.—S. J., a 5½-year-old white male, was under hospitalization for a disseminated granulomatous disease which was at that time considered to be on an infectious basis. Innumerable attempts to isolate an etiological agent had been made without success. Superinfection of draining cervical nodes had occurred several times with coagulase-positive staphylococci. These infections had been treated at one time or another with all available antibiotics. The patient had received antituberculous therapy for several months without benefit. It was decided to give this child a therapeutic course of novobiocin. He was started on 30 mg. per kilogram per day and this had been continued for seven days when he developed a generalized pruritic maculopapular eruption and an elevated temperature which were considered due to novobiocin. The antibiotic was immediately discontinued, and the rash faded over a period of several days. About one month later, some ten days following an exploratory thoracotomy for what proved to be a similar granulomatous process involving the mediastinum and the right middle lobe, it was decided to resume his antituberculous therapy and to include an antibiotic that would be effective against the staphylococci. Before other therapy was resumed, however, he was given one oral dose of novobiocin (250 mg.). On this occasion he developed, several hours after its administration, a generalized pruritic erythematous eruption associated with edema of the face, hands, and feet. Fever was again noted. The eruption cleared spontaneously over a period of several days. The child was subsequently given an intracutaneous injection of 40 gamma of novobiocin, with the immediate appearance of a 2 cm. area of erythema and faint central whealing which faded within an hour. No eosinophilia or neutropenia was noted. No measurements of indirect bilirubin were made.

Comment.—This child had, on two occasions, unequivocal sensitivity reaction due to novobiocin. This was associated with an immediate type sensitivity reaction on intracutaneous testing with novobiocin.

CASE 2.—N. V., a 15-year-old white female, was referred to the University of Minnesota Hospitals with a diagnosis of staphylococcal empyema. Six

weeks prior to admission here she had developed symptoms consistent with pneumonia for which she was treated at home by her mother with erythromycin and sulfadiazine. One week before being admitted to this hospital the patient was seen by a private physician because of a persistent cough which was productive of greenish sputum, pleuritic pain, and mild elevations of temperature, which had been occurring daily. By physical and x-ray examination she was considered to have a right-sided empyema. A thoracentesis was performed and cultures of the material obtained grew a coagulase-positive staphylococcus. She was treated with penicillin and streptomycin for a period of five days. For the two days prior to admission, erythromycin was added to the regimen. After this period of time, it was felt that the child would probably require surgical drainage and was referred to this hospital.

Examination on admission revealed findings which confirmed the admitting diagnosis. Approximately 100 c.c. of greenish purulent fluid was obtained from the right side of the chest on thoracentesis. Cultures of the material were sterile but Gram smears revealed the presence of gram-positive cocci in pairs and clusters. With this information as a guide to antibiotic therapy the patient was started on a course of erythromycin. She continued, however, to run a low-grade febrile course and because of this, novobiocin (35 mg. per kilogram per day) and neomycin inhalations were begun on the sixth hospital day. No improvement was noted and she maintained a febrile course, continued to feel weak, and complained of pleuritic pain. After seven days of this combined therapy, she developed an erythematous blotchy eruption over the entire body. This was most severe over the face and neck. The temperature rose to 104.2° F. and she continued to run temperature elevations higher than had been recorded for several days. Novobiocin was promptly discontinued and she was given Benadryl. The treatment was not otherwise altered. The eruption cleared gradually over several days. Later a skin test was performed with novobiocin which was without evidence of reaction over the next hour. No eosinophilia or neutropenia was noted at the time of the reaction. No measurements of liver function were made. Surgical drainage was subsequently required and the child improved slowly over a period of several months.

Comment.—This child's sensitivity reaction developed while she was receiving two antibiotics. The only modification of her treatment program was to discontinue the novobiocin. The manifestations then cleared spontaneously. We would attribute the reaction to novobiocin.

CASE 3.—C. D., a 6-year-old white female, suffered an extremely complicated course following the repair of an intraventricular septal defect and subsequently died some three months following surgery.

For an illness which was seriously considered to be subacute bacterial endocarditis she was receiving intensive treatment with large doses of penicillin. She had been essentially without improvement for a month when therapy was begun with novobiocin (40 mg. per kilogram). Both penicillin and novobiocin were being used in combination when seven days after initiating treatment with this new drug a generalized pruritic maculopapular eruption developed. Dermal wheals developed over the back. The eruption cleared gradually over a period of six days following cessation of treatment with both antibiotics. No increase in the febrile course was noted at the time of the reaction. No abnormalities were noted in the peripheral blood at this time. No liver function tests were performed at the time of the reaction. A few weeks later this child was given another course of penicillin therapy without event.

Comment.—This child's sensitivity reaction might have been due to either novobiocin or penicillin. She subsequently received further penicillin without any untoward reaction. We would therefore consider this reaction due to novobiocin.

CASE 4.—S. R., a 14-year-old white male, was in good health until approximately forty days prior to his admission to the University of Minnesota Hospitals, when he developed intermittent febrile episodes with occasional spikes of fever to 104° F. Associated with the fever he complained of generalized weakness, swelling of the left wrist, and a migratory serpigenous rash. He also had mild aching pains in the neck, both knees, arms, and ankles. There was occasional thoracic pain on deep inspiration and intermittent vague abdominal pain during this time. Two weeks after the onset of these complaints he was admitted to the local hospital, where a provisional diagnosis of a generalized septic process or acute rheumatic fever was made. No further significant information was obtained in the history at this time. Physical examination revealed a temperature of 104° F., with a mild tachycardia and a slight increase in the respiratory rate. Blotching of the skin was noted which was later described as being purpuric-like. No abnormalities of the joints were noted. No abdominal organs were palpable. His hospital course was characterized by extremely high, spiking, septic-type temperatures ranging in the evening hours to 104° or 105° F. and returning to near-normal values in the early morning hours. Laboratory examinations on admission to his local hospital revealed a sedimentation rate of 4 mm. in one hour and a hemoglobin of 10.5 grams per cent, with a white blood count of 9,600 (77 per cent polymorphonuclears, 18 per cent lymphocytes, 4 per cent monocytes, 1 per cent eosinophils). A blood culture taken on admission became positive on the sixth day, yielding an organism considered to be a pleomorphic streptococcus. This was subsequently identified at another laboratory as *Corneybacterium pyogenes.* Agglutinations for typhoid, paratyphoid, Pasteurella, and brucella were negative as was a heterophil determination. These were subsequently repeated but were still negative. The serum bilirubin at this time was 0.75 mg. per cent total, the thymol turbidity 3.5 units and the cephalin cholesterol flocculation 2 plus in forty-eight hours. The patient was treated with large doses of chlortetracycline without any change in the febrile course. Antibiotic therapy was then changed to large doses of tetracycline and penicillin. On the third day of hospitalization another blood culture was drawn and subsequently a growth of an undetermined variety of streptococcus was isolated. Disk-type sensitivity studies were interpreted as showing sensitivity only to novobiocin. Prior to the results of the sensitivity studies the dosage of penicillin was increased to 4,000,000 units a day without apparent benefit. After four days of this therapy, cortisone was started. The patient received 300 mg. daily for the first two days and then the cortisone was continued at 100 mg. a day for another nine days. Following the institution of cortisone therapy an immediate dramatic improvement was noted. With the report of the last blood culture and the results of the sensitivity studies he was started on novobiocin and the cortisone was discontinued. He received 2 Gm. every twelve hours orally for a total of eight days. On the sixth day of treatment with novobiocin he became icteric. This increased markedly over the next two days. Following the onset of jaundice he developed a purpuric type of skin rash. Novobiocin was discontinued at this time and he was again placed on cortisone. Liver function studies following the onset of jaundice revealed a direct bilirubin of 6.2 mg. per cent with a total of 13.6 mg.

per cent and a thymol turbidity of 13 units. Because of rapid deterioration in his condition the boy was transferred to the University of Minnesota Hospitals four days after the onset of jaundice.

On admission to this hospital the patient was extremely drowsy and displayed an orange-yellow discoloration of the skin. He had lost approximately 25 pounds over the last few weeks (three or four) prior to admission. He was intensely jaundiced, quite weak, and lethargic. The blood pressure was 80/60. There was a petechial rash over the lower extremities and a slightly papular erythematous rash over the trunk. There was a moderate degree of lymphadenopathy involving the axillary, inguinal, and cervical nodes. The liver was palpable approximately 1.5 cm. below the right costal margin in the midclavicular line. The tip of the spleen was palpable at the left costal margin. There was 2 plus pitting edema of the lower extremities. Neurological examination was not remarkable except for the changes in the sensorium previously noted.

Laboratory examinations revealed a hemoglobin of 10.3 grams per cent, with a white blood count of 17,400 (81 per cent polymorphonuclears, 17 per cent lymphocytes, 2 per cent monocytes) and a sedimentation rate of 10 mm. in one hour (Westergren). Urinalysis showed a 1 plus albuminuria and a positive qualitative bilirubin. Serum proteins revealed a total protein of 5.5 grams per cent, with an albumin-globulin ratio of 2.5:3.0. An electrophoretic pattern did not contribute any further useful information. The serum bilirubin was 14.8 mg. per cent direct reacting with a total of 25.8 mg. per cent. Total lipids were 52 units, thymol turbidity 10 units, and a cephalin cholesterol flocculation 3 plus. The CO_2 combining power was 20 meq. per liter, the sodium 128 meq. per liter, the potassium 5.5 meq. per liter, and the chloride 82 meq. per liter. The BUN was 52 mg. per cent. A prothrombin time was 30.8 seconds with a control of 14.4 seconds, and both the bleeding and the clotting time were greater than 15 minutes. A blood culture was subsequently reported as sterile. Bone marrow examination did not contribute further information and a culture of this material was sterile. Agglutinations for typhoid, paratyphoid, brucella, Pasteurella, and proteus OX_{19} and OX_2 were all negative. The C-reactive protein was 2 plus. An ASO titer was 50 Todd units.

Intravenous fluid therapy and antibiotics were started on admission (penicillin and Chloromycetin). His condition remained stable until about thirteen hours after admission, when he became severely hypotensive. He was given 100 mg. of hydrocortisone hemisuccinate intravenously and the blood pressure became stabilized at approximately the level present on admission. He died twenty hours after admission.

Post-Mortem Examination.—Gross examination of the body demonstrated those findings present on admission. The petechial rash, however, had spread to involve the entire cutaneous surface. On opening the body there was 150 c.c. of dark bile-stained fluid in the peritoneal cavity. The left pleural cavity contained approximately 500 c.c. of dark brownish fluid. The pericardial sac contained 35 c.c. of dark brown, clear fluid. The heart appeared grossly normal, but on cut section there were occasional small areas of hemorrhage scattered throughout the musculature. The lungs were reddish purple and mottled. The tissues all appeared bile stained. Cut sections of the lungs were excessively moist with serosanguineous exudate. On opening the gastrointestinal tract, irregular mucosal hemorrhages up to 5 cm. in diameter were scattered throughout the stomach and both small and large bowel. All of these tissues were somewhat edematous. The liver weighed 1,940 grams. There were small, irregular, subscapular, bluish areas suggesting congestion.

The edges were slightly rounded. On cut section there was evidence of passive congestion, with stellate streaks of a reddish color radiating from the central portion of the lobules. There was a muddy tan appearance to the liver parenchyma which was more prominent in the central areas of the lobules. The gall bladder was markedly edematous and semitranslucent. No stones were found. All bile ducts were patent, and there was no evidence of obstruction in the hepatic or common ducts. At the junction of the pancreatic and common bile ducts there were numerous soft, discrete lymph nodes which, however, did not obstruct either duct. The spleen weighed 900 grams and was light red. There was no evidence of infarction. On cut section the corpuscles were visible but appeared somewhat reduced in number, while the trabeculi appeared somewhat more prominent than usual. Bile staining and occasional small hemorrhagic areas were noted in both kidneys. All the lymph nodes examined appeared enlarged. These included the tracheobronchial nodes, those about the pancreatic duct and the common duct, the celiac and the periaortic groups. Microscopic examination of the pathological material showed pulmonary edema, myocarditis, diffuse lymphoid hyperplasia, and a picture of acute diffuse hepatic necrosis. The lungs were markedly congested with dilatation of all the vessels and collections of fluid within the alveoli, but there was no evidence of acute inflammatory disease. Sections of the myocardium revealed some edema between the muscle fibers and occasional fragmentation of the fibers. No Aschoff bodies were found. Scattered areas of focal necrosis were present. Except for some cloudy swelling of the tubular epithelium the kidneys were histologically normal. There was questionable slight thinning of the adrenal zona glomerulosa, probably reflecting treatment with steroid hormones. The spleen revealed a picture of congestion in which the sinusoids were distended with masses of red cells and leukocytes. The pulp was increased in quantity and the fibrous trabeculi appeared diminished. The germinal centers were poorly distinguished and diminished in number. Reticulum cells predominated though there were occasional mature lymphocytes. The sinusoidal epithelium appeared swollen. Rather frequent megakaryocytes were present but no abnormal cells were seen. The distinguishing feature of all the lymph nodes was thought to be one of lymphocytic depletion, as though production of lymphocytes had ceased. Large reticulum cells predominated and only a very occasional, poorly formed germinal center was visible. The lymph spaces were distended with macrophages and in some areas these cells contained blood pigment. Numerous megakaryocytes and rather frequent immature cells of the granulocytic series were visible. Liver sections revealed a generalized destructive process in all sections. The architecture of the liver was greatly distorted. Lobules were difficult to recognize and the portal spaces were equally difficult to locate. There was widespread irregular necrosis which, in some areas, involved the central portion of the lobule more than the peripheral portion. The sinusoids were filled with cellular debris and masses of red cells. In an occasional area attempted regeneration was evident. In all areas, golden-brown pigment granules appeared within the hepatic cells that remained. There were occasional focal collections of inflammatory cells consisting principally of lymphocytes and an occasional plasma cell. Only very rare polymorphonuclear leukocytes were seen. This inflammatory cell exudate was principally in the areas of the portal triads, but appeared to some extent around the central veins. No significant changes were present in the gall bladder or the pancreas.

Comment.—On final consideration of all of the aspects of this rather complicated illness, it was our feeling that this boy was initially suffering

from what was most probably juvenile rheumatoid arthritis and that the acute diffuse hepatic necrosis and generalized lymphoid hyperplasia could most logically be attributed to sensitivity to novobiocin.

DISCUSSION

The cutaneous manifestations of sensitivity to novobiocin have been previously recorded in the literature. They are, in general, similar to those that we have observed. To our knowledge, however, there has not been a case reported in which death might be attributed to this drug. Acute toxicity studies in dogs[2] at a dosage level of 300 mg. per kilogram per day administered intravenously has resulted after two to four days in severe prostration. After sacrificing these animals, necropsy revealed severe degenerative changes in the liver and kidneys. Congestion and hemorrhage were also noted in the gastrointestinal tract. Over a sixty-day period at this dosage level, given orally, moderate Bromsulphalein retention occurred in two out of three dogs. Intravenous administration at levels of 200 mg. per kilogram has consistently produced hemoglobinemia. Minor elevations in direct bilirubin have been mentioned in one clinical report where these determinations were performed as part of the study. It does not seem inconsistent with these observations to attribute certain events occurring in our fourth case to sensitivity to novobiocin and the ultimate death of this patient to its continued administration.

CONCLUSIONS

On the basis of our own observations and those already present in the literature, novobiocin would appear to be an appropriate antibiotic for use in the treatment of certain gram-positive infections. It is not without danger, however. The high incidence of sensitivity reactions which have been observed and the one death recorded in our present report, which may be attributable to novobiocin, should be considered before this new drug is given wide clinical application.

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THE "GROWTH SPECTRUM": A SIMPLIFIED CHART FOR ASSESSMENT OF GROWTH

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THE classic and perhaps simplest technique for evaluating the nutritional and developmental status of a child utilizes chronologic measurements of body weight and height. Unsatisfactory growth and development is frequently the initial (and sometimes the only) overt manifestation of undernutrition or disease.

It is now generally recognized that the practice of comparing children according to *average* heights and weights is not only physiologically invalid but often psychologically detrimental. As has been aptly emphasized, "it is more important to know that a child is consistently maintaining a given relationship (in height and weight) to other children of his sex and age than it is to know that he is tall or short."[1] Implicit in this statement is the need for defining the child's individual physique and for determining whether his rate of growth conforms to the developmental pattern of his specific physique. Wetzel states it succinctly when he says that the fundamental tenet of growth assessment is comparison with self.[2]

THE "GROWTH SPECTRUM"

In an effort to provide a simplified technique for assessing growth and development, the "Growth Spectrum" (Fig. 1) has been devised. This is a chart in which the weight-height-age relationship for each sex is visually emphasized by differently colored zones or patterns of growth. The colored zones serve the same function as percentile ratings or channels on conventional height-weight charts, that is, a mechanism for the establishment of a growth pattern as compared to the rest of the population of the same age and sex.

Because of the desirability of using children reared under reasonably ideal conditions for comparison purposes, the statistical data on which the Growth Spectrum is based were obtained from published authoritative surveys[3-5] among white children of northern European ancestry and a high socioeconomic level. Although such children tend to be above national "averages," the Growth Spectrum should accommodate approximately 90 per cent of the pediatric population.

The Growth Spectrum enables one to estimate individual physique. A child may be inherently slender or stocky, if his weight and height are not in corresponding color zones. However, marked disparity between weight and height color zones suggests a need for clarification of the discrepancy. This device also provides a simple means of "graphing" growth curves without the use of individual growth charts, and of visualizing deviations

From the Medical Research Department, White Laboratories, Inc.

GROWTH SPECTRUM

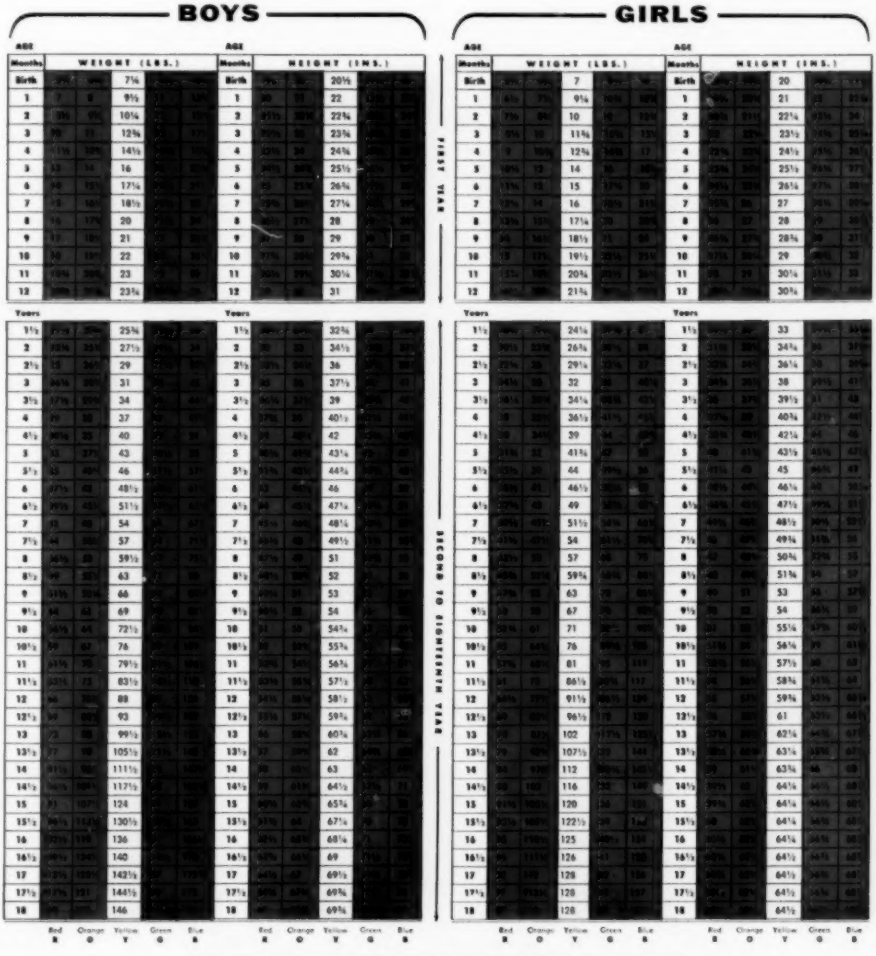

Fig. 1.—The "Growth Spectrum." (Reduced to one-fourth actual size.)

from specific patterns of growth. Each color zone represents a growth zone or pattern. Generally, a healthy child will remain in the same weight and height color zones from age to age. An abrupt or a slow, but continuous shift from one color zone to another indicates an altered trend in growth and suggests that the cause be investigated.

The simple directions for use of the Growth Spectrum are reproduced below:

(1) Determine child's weight and height.

(2) Find color zones *closest* to the weight and height measurements for the child's sex and age.

(3) When recording weight and height, also record color zones. For example:

Weight: 37 pounds—Y (for yellow zone)

Height: 37½ inches—O (for orange zone)

(4) Subsequent weight and height measurements must be made at periodic intervals to indicate whether the child is adhering to a specific growth pattern (color zone). Note: Measurements made during illness or shortly thereafter are not satisfactory for judging a child's build.

Perusal of previous weight and height color zone notations in the child's health record quickly indicates degree of adherence to his former pattern of growth.

In order to test the utility and simplicity of the Growth Spectrum, fifty-five physicians (forty-five pediatricians and ten general practitioners) were asked to evaluate the chart in office practice. The results indicated a high degree of physician acceptance. After six or more months of practical experience with the Growth Spectrum, forty-nine of the fifty-five physicians reported their regular and continued use of the chart, and expressed the opinion that it should be made available to the medical profession.*

THE "GROWTH SPECTRUM" AND PREDICTION OF MATURE PHYSICAL DIMENSIONS

The physician is called upon occasionally to predict the adult physical dimensions of a child. In response to this need, Kowaloff[6] recently published a series of five simple formulas for predicting mature height, weight, and pelvic breadth from corresponding measurements in early childhood. Similar relationships have appeared previously in the literature on growth appraisal.[1] The Growth Spectrum circumvents one obvious limitation of such devices: the need for dimensional information at a specific age. When using the Growth Spectrum for prediction, an estimate of adult height and weight can be made at any age, provided serial measurements during health have delineated the height and weight color zones. Extrapolations to maturity are then made within the appropriate color zones. This technique also obviates the need for formula memorization and arithmetic manipulation.

GROWTH: THEORETICAL CONSIDERATIONS

Growth—Huxley's "self-multiplication of living substance"—has always evoked the interest of the savant (for theoretical reasons) and the "practitioner" (for practical ones). Although growth *assessment*, the topic of this discussion, implies the practical

*Copies of the "Growth Spectrum" currently may be obtained by physicians from White Laboratories, Inc., Kenilworth, N. J.

utilization of growth data, it seems appropriate to review briefly several basic principles governing the growth and development of all biologic matter.

Historically, the study of growth started with gross observations of total or cumulative growth followed by investigations of units of ever-decreasing size: organs, tissues, cells, cell constituents, and molecules. As our knowledge and experimental approaches matured, our study of units of smaller size and diminished complexity followed a pattern of "evolution in reverse."

It is to be emphasized, however, that the smooth S-shaped curve is a result of a mathematical averaging of many sets of data and is not usually descriptive of a single case. By plotting human growth curves it can be seen that the weight curve is proportional to the height cubed (weight $\cong$ height^3) since height is a linear function whereas weight is proportional to volume, a cubic function.[7]

The sigmoid growth curve has a segment of increasing slope (Fig. 2, *A*) separated by an inflection point from a segment of decreasing slope

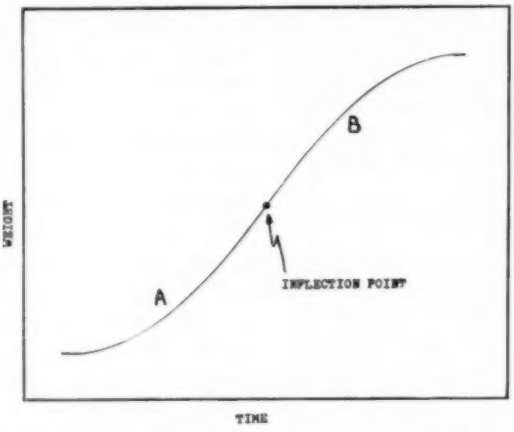

Fig. 2.—Sigmoid curve describing the growth of individuals or populations.

In investigations of the characteristics of cumulative growth, its motion is frequently described by plotting a growth curve with weight or height on the vertical axis (ordinate) and time on the horizontal axis (abscissa). The resulting curve is S-shaped (Fig. 2) and describes the growth of populations or individuals (which are, after all, *populations* of cells) be they plants or animals. This sigmoid curve describes the growth of human beings, populations of fruit flies, or maize. (Fig. 2, *B*). The curve parallels the horizontal axis upon attainment of mature body size and weight. The first segment of the curve describes the more or less uninhibited growth occurring between infancy and puberty, while the second portion represents the period between puberty and senescence in which growth is subject to inhibitory pressures. The point of inflection is the time at which acceleration in the growth rate is zero since no velocity *change* occurs. This transition from

increasing to decreasing growth velocity is typified by the most rapid weight gains because the velocity of growth is at a maximum at this time. The inflection point represents puberty in animals, flowering in plants, and the "coming of age" in populations.[8]

The most striking distinguishing characteristic of the human growth curve is the unusually long period between weaning and puberty. The exceptionally long infancy in human beings distinguishes man from other animals who have a proportionately shorter "dependent" period. This disparity in the duration of dependence can be examined by comparing the percentage of the mature weight achieved by different species at puberty, a time of developmental equivalence. Many mammalian species reach approximately one-third of their mature weight at puberty. The percentage of mature weight achieved at the inflection point by children with differing physiques is plotted in Fig. 3 against the age at which the inflection occurs. The data for these curves were obtained from a graphic representation of the weights in the Growth Spectrum.

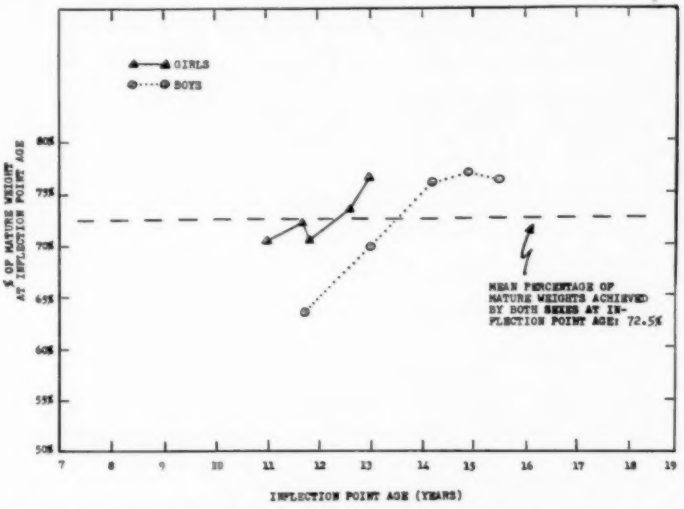

Fig. 3.—The percentage of mature weight achieved at the inflection point by children with differing physiques.

It is clear that man attains a greater proportion of his mature weight at puberty than other species. The following other conclusions regarding the development of children result from an examination of Fig. 3:

(1) The inflection point usually occurs between 11 and 13 years for girls and between 11.5 and 15.5 years for boys.

(2) At the inflection point the girls weigh 70 to 77 per cent of their mature weight, while the boys reach from 63 to 77 per cent of their adult weight.

(3) The mean percentage of the mature weights achieved by both sexes at the inflection point is 72.5 per cent.

Once again it is to be stressed that the pattern which evolves from studying the weight data of the Growth

Spectrum results from an averaging process. Individual variations in specific cases do not necessarily indicate unsatisfactory health or progress, although wide deviations should prompt a search for the cause.

SUMMARY

The Growth Spectrum, a new chart which simplifies the assessment of growth and development and the prediction of adult physical dimensions, has been described. This chart visually emphasizes different patterns of growth by utilizing several colored weight and height zones. The Growth Spectrum enables the physician to define the child's individual physique and to determine whether his rate of growth conforms to the developmental pattern of his specific physique. This technique simplifies record-keeping by eliminating the need for maintaining and filing an individual growth chart for each child.

I wish to express my appreciation to Dr. Edward R. Neary for advice and assistance in the design of the "Growth Spectrum" and the preparation of this manuscript.

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Of Canker in the Mouth

Many tymes by reason of corrupcion of the milke, venomous vapours arising from the stomake, & of many other infortunes there chanceth to breede a canker in the mouthes of children, whose signes are manifest ynough that is to say, by stinkyng of the mouth, peine in the place, continuall renning of spittle, swellyung of the cheke, and when the mouth is opened against the sonne, you maye see clerelye where the canker lyeth. It is so named of the latter sort of phisicions, by reason of crepynge and eatyng forwarde and backwarde, and spreadethe it selfe abrode lyke the feete of a creues, called in latine cancer, notwithstandyng I knowe that the Grekes, and auncient latynes, gyve other names unto thys dysease, as in callyngr it an ulcer, other whyles aphthae, nome, carcinomata, and lyke, whiche are all in englyshe knowen by the name of canker in the mouthe, and although there by many kindes according to the matter, whereof they be engendred, & therfore require a diversitie of curyng, yet for the moste parte, whan they be in children, the cure of them all differeth very little or nothyng, for the chiefe entent shall be to remove the malignitie of the sore, and to drie up the noysome matter and humours, than to mundify & heale, as in other kyndes of ulcers.

FROM THOMAS PHAIRE'S THE BOKE OF CHYLDREN, 1544.

EARLY MYOSITIS OSSIFICANS PROGRESSIVA OCCURRING IN HOMOZYGOTIC TWINS

A Clinical and Pathologic Study

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C. William Daeschner, M.D.
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MYOSITIS ossificans progressiva is a rare disease characterized by exaggerated proliferation of connective tissue in the interstitial tissue of skeletal muscles and in fascia, tendons, ligaments, and aponeuroses, with eventual progression into extensive dystrophic calcification and ossification. In most patients with the disease, there have been certain associated congenital anomalies, notably microdactyly of the great toes and thumbs with ankylosis of the interphalangeal and metatarsophalangeal joints. There is frequently absence of one phalanx. Other digits may be involved as well.

This condition was first described by Patin[2] in 1692, and since that time some 180 cases have been recorded. Among these the disease has been reported only once in homozygotic twins.[4] Herein is reported the second instance of myositis ossificans progressiva in homozygotic twins. These siblings are of additional interest because they presented with early manifestations of the disease and the process was studied anatomically as well as clinically.

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CASE REPORTS

Case 1.—Jimmie L., a 19-month-old Latin American male, was admitted to Jefferson Davis Hospital on June 23, 1954, for diagnostic study. The mother had observed that the infant had had two "swellings" in the occipital region, present since birth. His neck had always been stiff and he could not move his head to either side. About three months prior to admission the muscles in the back of his neck became very firm and gradually stony hard. Small lumps appeared periodically over the back of his head, disappearing after several days. About ten days before admission the swelling over the posterior neck began to enlarge rapidly.

The patient was one of homozygotic twins born at this hospital. The twins were the products of the seventh pregnancy of their mother. The patient weighed 7 pounds 6½ ounces at birth. No neonatal distress or complications were present. The dietary regimen was apparently adequate. The infant sat alone at 4 months and stood alone at 9 months. He had never been able to walk alone, and he always seemed to have weak legs. His first tooth appeared at 4 months.

Review of his clinic record revealed that he was first brought to the pediatric clinic at the age of 5 months. At that time a swelling, not otherwise described, was noted in the occipital region. Radiographs revealed soft tissue swelling in the posterior neck.

There was no calcification. No abnormalities were present in the bones of the skull. Several additional radiographs of the skull and chest revealed nothing more. At the age of 9 months he was admitted to the hospital for correction of bilateral hallux valgus.

On admission at the age of 19 months the infant appeared somewhat obese. His face was rounded. He did not appear acutely ill. There were swelling and deformity of the neck and he maintained his head in a slightly flexed position with the chin turned to the left. Temperature was 99.4° F. (R), respirations were 28 per minute, and pulse was 100 per minute. Fronto-occipital circumference of the head was 49 cm. Chest circumference was 57 cm. Length was 84 cm., and weight was 13 kg. (height and weight in ninetieth percentile for age).

There was stiffness of the neck with limited rotation to right and left and inability to flex the chin onto the chest. An irregular hard mass was present over the right side of the neck, extending from the mastoid process down to the supraclavicular fossa and posteriorly to the spinous processes. The mass was not movable and seemed fixed to the deep structures. There was microdactyly of the thumbs and great toes. The thumbs were quite short (Fig. 1). Well-healed incisional scars were present along the medial aspects of the great toes.

Laboratory studies during hospitalization revealed a normal urine and a negative serologic test (VDRL) for syphilis. The initial hemoglobin estimation was 6.5 grams per cent; this rose to 10 grams per cent after transfusion with 250 c.c. of whole blood. Hematocrit at that time was 35 vol. per cent. Total leukocyte count was 7,500 per cubic millimeter, with the following differential: neutrophilic granulocytes, 38 (35 segmented and 3 band forms); lymphocytes, 62. Blood urea nitrogen was 18 mg. per cent, serum phosphorus was 5.8 mg. per cent, and alkaline phosphatase was 2.6 Bodansky units. Serum calcium was 11.3 mg. per cent. Total serum proteins were 6.8 grams per cent (albumin, 5.3 grams per cent; globulin, 1.5 grams per cent). Erythrocyte sedimentation rate was 0 mm. in one hour. Blood group was O, Rh positive.

Fig. 1.—Jimmie L. There is microdactyly of the thumb and great toe.

The initial clinical diagnosis was "soft tissue sarcoma." A biopsy of a small lymph node in the right posterior cervical chain revealed no histologic change. The biopsy incision healed rapidly but, within thirty-six hours after the procedure, indurated swelling of the right neck and shoulder was noted. Six days later there had been extension of the process to involve the entire right side of the back to the level of the twelfth dorsal vertebra inferiorly and to the anterior axil-

Fig. 2.—Jimmie L. Extensive soft tissue swelling is present over the posterior neck and back. Swelling of the tissues surrounding the biopsy site on the right is even more marked.

lary line laterally. The swelling was quite firm and tender, was nonpitting, and there were no apparent inflammatory changes in the overlying skin. Motion of the neck in any direction was impossible and there was limited abduction of the right arm. A biopsy of the right mid-back was obtained. The amount of excised tissue was small. The left neck and shoulder had by this time become involved. A second generous biopsy specimen was obtained on July 11, 1954. This biopsy site became infected. From this site the same type of swelling developed (Fig. 2) and extended over to the left back until both sides were almost symmetrically involved.

On July 22, 1954, cortisone, 100 mg. daily, was begun by intramuscular injection. There was some decrease in extent of the swelling over the right side. The most profound change, however, was in the infant's mood, which changed from constant irritability to contentment within forty-eight hours. There was further gradual decrease in the swelling over the right side during the next week. The left side remained indurated. The biopsy site gradually healed. At the stage of most marked swelling radiographs revealed diffuse soft tissue density.

On Aug. 17, 1954, the swelling over the right back reappeared and rapidly enlarged. Intramuscular ACTH, 25 mg. every six hours, was given, beginning August 26. Some decrease in the swelling ensued. By September 2 there was no further clinical improvement and, because of marked decrease in the total eosinophil count, the ACTH was decreased to 15 mg. every six hours. The infant was discharged on Sept. 16, 1954, and steroid therapy was discontinued.

Case 2.—Johnnie L. was the 19-month-old homozygotic twin brother of Jimmie L. He was admitted on July 17, 1954, for study and observation, as a consequence of the established diagnosis of myositis ossificans progressiva in his twin.

His developmental history was almost identical with that of his brother. He also had been admitted at the age of 9 months for surgical correction of bilateral hallux valgus. He too had never been able to walk alone. The mother had not noted any stiffness of his neck, nor had any swelling been observed. No history of similar disease was known in other members of the family.

Physical examination revealed a male infant who did not appear ill. Temperature was 99.8° F. (R), respirations were 30 per minute, and pulse was 120 per minute. Fronto-occipital circumference of the head was 44.5 cm. Chest circumference was 50 cm. Weight was 11 kg. and height was 81 cm. (height and weight in fiftieth percentile for age).

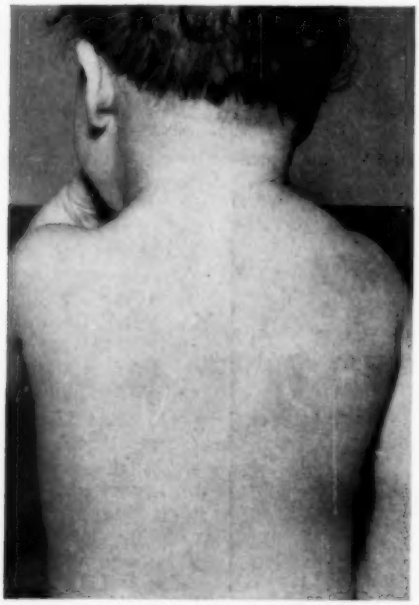

Fig. 3.—Johnnie L. The soft tissue swelling predominantly involves the right side of the neck and the right shoulder girdle and back.

Fig. 4.—Johnnie L. Compare with Fig. 1. The digital anomalies are identical.

There was definite limitation in lateral movements of the head. The muscles of the posterior neck and back were firm (Fig. 3). The teeth were small and wide apart with more than half of each tooth covered with gingiva. The thumbs were short with little or no movement of their distal phalanges. The great toes were short and incisional scars were present over their medial aspects (Fig. 4). There was an area of hyper-pigmentation over each lateral malleolus. No other abnormalities were observed.

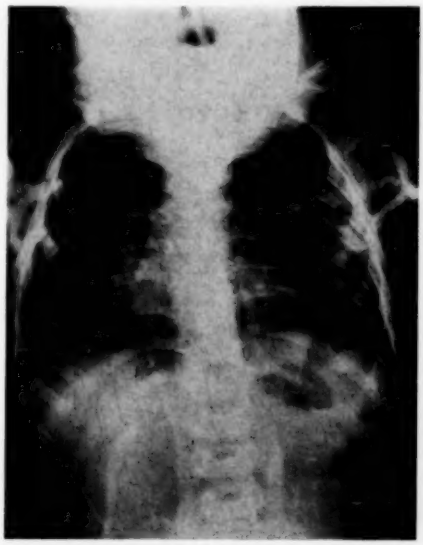

Fig. 5.—Jimmie L. Radiograph at age 42 months, twenty-two months after histologic diagnosis. Well-defined bands of ossification extends through the muscles around the shoulders and upper trunk and in the long muscles of the back.

Laboratory studies during hospitalization were quite similar to those observed in the twin. Initial hemoglobin estimation was 7.5 grams per cent, rising to 11.5 grams per cent after transfusion with 250 c.c. of whole blood. Erythrocyte sedimentation rate was 0 mm. in one hour. Blood urea nitrogen was 10 mg. per cent, serum calcium was 11.7 mg. per cent, serum phosphorus was 6.1 mg. per cent, and alkaline phosphatase was 4.3 Bodansky units. Serum proteins were 7.0 grams per cent (albumin, 5.8 grams per cent, globulin, 1.2 grams per cent). Blood group was O, Rh positive.

Tissue obtained by biopsy of a posterior cervical lymph node with adjacent muscle and overlying skin revealed no significant histologic change. Slight induration developed around the biopsy site. Because of the apparent excitation of the process in the twin brother following an extensive biopsy, it was elected not to risk aggravation of the process in this infant by taking another biopsy of the area.

Follow-Up.—The parents of these infants did not keep close follow-up clinic visits, although the infants were seen periodically after discharge. On

Fig. 6.—Johnnie L. Radiograph at same age as twin shown in Fig. 5. Ossification of muscles has a similar although slightly less extensive distribution.

June 6, 1955, the distribution of soft tissue changes was similar in the two, the only distinction being the more marked involvement in Jimmie L. There was thickening and induration of the posterior neck muscles, the paraspinous muscles, and the trapezius and latissimus dorsi bilaterally, extending to the level of the iliac crest. The right pectoralis major was slightly less involved. Additional radiographic studies revealed small, calcific, soft tissue deposits surrounding the greater

Fig. 7.

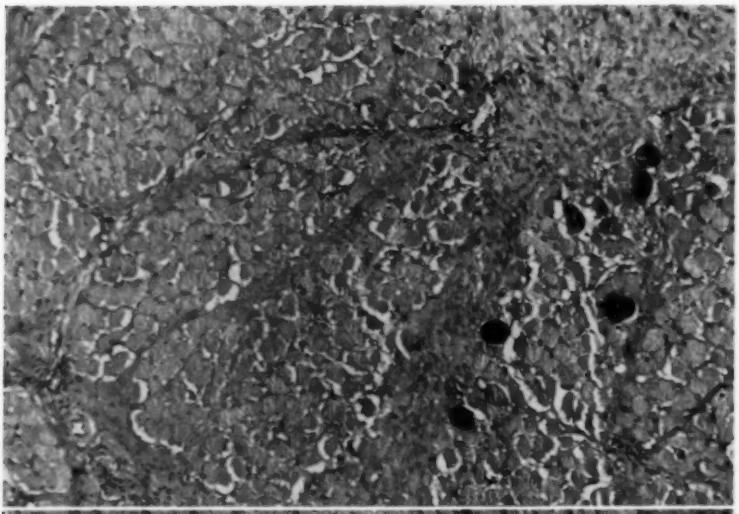

Fig. 8.

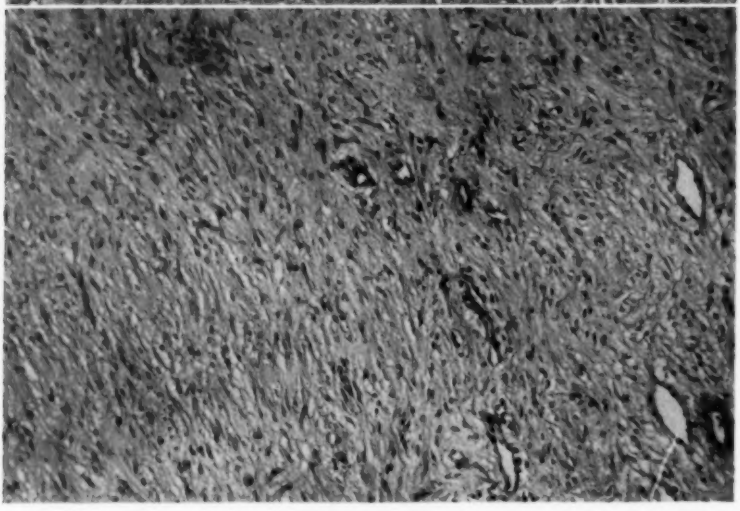

Fig. 7.—Early myositis ossificans progressiva involving skeletal muscle. Proliferating cellular connective tissue extends between muscle bundles. There is swelling of many muscle fibers with granularity of the sarcoplasm and some loss of striations. The deeper-stained muscle fibers are examples of hyaline degeneration. Scattered atrophic muscle fibers are present. (H and E; ×120; reduced ⅕.)

Fig. 8.—In an area of skeletal muscle adjacent to fascia, the connective tissue proliferation is extensive, and there is early deposition of collagen. Muscle fibers are not apparent. (H and E; ×120; reduced ⅕.)

trochanter in Johnnie L. No other soft tissue calcification was seen, nor was any evident in radiographs of the more severely involved twin. One other radiographic feature, not recorded previously, was the presence of bilateral deformities of the upper ends of the tibias in both children, interpreted as possible failure of tubulation.

When last observed on May 30, 1956, at the age of 3½ years, there was apparent decrease in bulk of tissue in the involved areas in both twins. Radiographs of Jimmie L. revealed ossification in the biceps muscles, particularly on the left, and extensive ossification involving the sternocleidomastoid muscles, the trapezius muscles, the muscles of the shoulder girdle, and the long muscles of the back (Fig. 5). Somewhat more irregular and less extensive ossification was present in radiographs of Johnnie L., involving the sternocleidomastoid muscles, the pectoral muscles, the posterior neck muscles and fascia, and the muscles of the right back (Fig. 6).

Pathology.—(Tissue obtained from Jimmie L). Grossly, the second muscle biopsy consisted of a segment of skin with attached subcutaneous tissue and skeletal muscle. The skin was not unusual. There was extensive firm, white thickening of the muscle and on the deepest surface there was a layer of dense white tissue about 0.2 cm. thick. Thick white fibers extended into the subcutaneous tissue.

Microscopically, changes were confined to the deeper portion of subcutaneous tissue and to the muscle layer. These consisted of broad infiltrating strands of newly formed, cellular connective tissue extending diffusely throughout the interstices, widely separating smaller muscle bundles and adipose tissue cells. In focal areas newly formed collagen deposits were apparent. Muscle fibers were in varying stages of degeneration and atrophy. No calcification was evident (Figs. 7 and 8).

DISCUSSION

The etiology of myositis ossificans progressiva is unknown. The most tenable concept is that it represents a hereditary disturbance in development and growth potential of the mesoderm. In support of this are the frequency of associated congenital deformities involving tissue of mesodermal origin, the onset early in life, and the occasional occurrence in twins.

The lesions develop in three more or less well-defined clinical stages which are correlated with the morphologic changes. Initially there is doughy swelling of the areas of involvement, generally beginning in the posterior neck and shoulder girdle. Histologically, in this stage, there is interstitial edema with marked proliferation of connective tissue (essentially a form of sclerosing edema). Muscle fibers incorporated in the process reveal various stages of degenerative and atrophic changes and are eventually replaced by the connective tissue. This stage, which may be classified as the acute phase, may be of relatively short duration. Low-grade fever, localized temperature increases over the involved areas, and associated tenderness are frequently present. These signs and symptoms gradually regress, although the indurated swelling usually persists. Histologically at this time there is more apparent collagenization of the connective tissue and it begins to fuse. This is a gradual process developing into the second stage. Eventually, dystrophic calcification develops in the involved areas and there is a particular tendency to ossification. With the conversion of the process into sclerotic

connective tissue and bone, the involved areas become rigid and there are generalized ankyloses and synarthroses in the end stage.

During the progress of the disease trauma may initiate recurrences of the acute phase or progression to involve additional structures. This is well illustrated in the first of the twins herein reported in whom marked accentuation of the process developed following biopsy of an involved area. Trauma certainly cannot be considered more than a stimulating factor. In the localized or circumscript form of myositis ossificans, trauma seems to be a frequently associated factor in the development of the lesion. The early histologic changes of traumatic myositis ossificans are identical to the changes observed in the present cases. This localized lesion, particularly, may be mistaken histologically for a soft tissue sarcoma, usually a fibrosarcoma. Although the same histologic misinterpretation might well be made with the progressive form, the frequent association of other abnormalities should aid in establishing the diagnosis.

There is no satisfactory therapy and the disease progresses gradually until the process involves almost all the skeletal connective tissues and muscles of the body, literally converting the individual to bone. ACTH and cortisone appear to have a temporizing effect on the acute phases of the disease, as was noted in the present cases. It is doubtful whether prolonged use of steroid therapy, even when begun early, will modify the ultimate course.

The clinical features of this disease have been more extensively reviewed in the recent literature by Lockhart and Burke, and the radiographic features by Singleton and Holt.

SUMMARY

The clinical and pathologic findings in early myositis ossificans progressiva occurring in homozygotic twins are presented. This is the second reported instance of this disease in identical twins.

The early lesions consist of marked interstitial edema and connective tissue proliferation in the involved mesodermal structures. Degenerative changes in the skeletal muscle fibers are probably secondary to the surrounding connective tissue reaction.

The progress of the disease appears to be unaffected by steroid therapy, even when instituted early, except for a transient response during the more acute phases.

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RECOVERY FROM MECONIUM PERITONITIS ASSOCIATED WITH A DIAPHRAGM-LIKE OBSTRUCTION OF THE PREPYLORIC MUCOSA

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MECONIUM peritonitis is a foreign-body and chemical peritonitis caused by the escape of sterile meconium through a bowel perforation occurring in utero or very shortly after birth. The perforation may be due to increased intraluminal pressure proximal to a congenital or acquired obstruction, to direct trauma to a viscus or to spontaneous perforation of localized defects in the wall of the intestine.

Simpson[9] in 1838 first reported and reviewed a series of twenty-five cases of meconium peritonitis. Low and associates[8] in 1949 found more than 100 reported cases, with few survivals. Recently, White[10] in a brief review reported eighteen survivals in the literature following operative treatment of meconium peritonitis. This case is felt to be worthy of report because it is the nineteenth reported survival and because of the seemingly unique nature of the obstruction.

CASE REPORTS

A gravida iv, para iii white female was admitted in active labor to Fitkin Memorial Hospital, Neptune, N. J., on April 30, 1956. Prenatal history was essentially normal. Her blood type was A, Rh positive. The infant was delivered spontaneously following eight and one-half hours of a normal labor. Birth weight was 10 pounds, 8 ounces.

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Immediately following delivery, the infant was cyanotic, dyspneic, and the abdomen distended. It was noted particularly that in addition to the abdominal distention the abdominal subcutaneous tissue felt indurated and tense. Scrotal edema was also present. At 6 hours of age the infant was seen by one of us. At that time the physical examination was as previously described except that the respirations were retracting and edema of the upper lids and feet was noted. The infant was placed on oxygen and suction with elevation of the head. Antibiotics were administered and feedings withheld. Immediate blood typing and Coombs testing were noncontributory. The infant's condition remained critical.

X-ray at 26 hours of age was characteristic of meconium peritonitis (Fig. 1). After surgical consultation the infant was prepared for laparotomy. This was performed through a right rectus incision. The abdomen was found to contain 300 to 400 c.c. of clear yellow fluid containing flecks of meconium. The viscera were covered by an adherent plastic exudate so that initially no recognizable structures were encountered. Careful dissection and piecemeal removal of the exudate demonstrated the distal portion of the stomach, duodenum, small intestine, liver, gall bladder, spleen, and both kidneys to be normal in position and disposition. The cecum was in the right upper quadrant. The transverse, ascending, descending, and sigmoid colons were normal. There was no evident defect in the intestinal tract. Saline solution injected into

the stomach through a needle distended the duodenum and first portion of the jejunum. Because the gastrointestinal tract was considered intact below the ligament of Treitz, a Witzel type jejunostomy using a No. 8 rubber catheter was performed, the catheter being brought out through the upper end of the wound. The wound was closed with interrupted silk sutures.

Postoperative nutritional status was maintained by jejunostomy feedings fairly well, except for somewhat loose stools. Antibiotics and blood were administered supportively. But soon the

Fig. 1.—X-ray of abdomen at 26 hours of age, demonstrating irregular areas of calcific density and hydropneumoperitoneum.

infant began to have bile-stained vomiting, and at times regurgitation of almost unchanged jejunostomy feedings. When oral feedings were attempted they were promptly regurgitated intact. Barium administered per gastric tube demonstrated a high degree of gastric retention due to an obstruction involving the prepyloric portion of the stomach (Fig. 2). The nature of the obstruction was obscure.

At 3 weeks of age the infant was re-explored through a left upper rectus incision. There was residue of the plastic peritonitis. On palpation the stomach, pylorus and duodenum were normal except for hypertrophy of the gastric musculature. Attempts to guide the tip of a nasogastric tube through the pylorus were unsuccessful. A short longitudinal gastrotomy was made and a Crile hemostat introduced toward the duodenum. Passage was prevented by an apparently complete obstruction. On lengthening the gastrotomy a diaphragm-like disposition of the gastric mucosa was noted immediately proximal to the pylorus, in which there was an opening 5 mm. in diameter. A large flap of gastric mucosa arising from the posterior surface of the antrum formed an effective one-way flap valve. The tip of the hemostat could be easily passed into the duodenum under direct vision. The gastrotomy was continued across the pylorus for a distance of about 3 cm. The gastric tube was passed into the duodenum and the gastroduodenal incision was then closed transversely (Fig. 3).

Postoperative course was uneventful. Antibiotics, blood, and intravenous fluids were continued for several days. Forty-eight hours after the operation oral feedings were gradually introduced. The infant was discharged at 6 weeks of age weighing 8 pounds, 13 ounces. Three months later at the age of 4½ months the infant weighed 13 pounds, 11 ounces and was progressing normally.

DISCUSSION

The extreme rarity of meconium peritonitis is demonstrated by the report of Bendel and Michal.[1] In a fifteen-year period, 1937 to 1952, only three cases of meconium peritonitis were diagnosed at the Charity Hospital in New Orleans out of 853,293 admissions and 108,744 live births. In a recent report by White[10] of eighteen survivals in the literature, an obstruction was found in eleven infants. In the greater number of cases the perforation was associated with obstruction due to atresia of the small bowel, inguinal hernia, imperforate anus, volvulus, or meconium ileus.

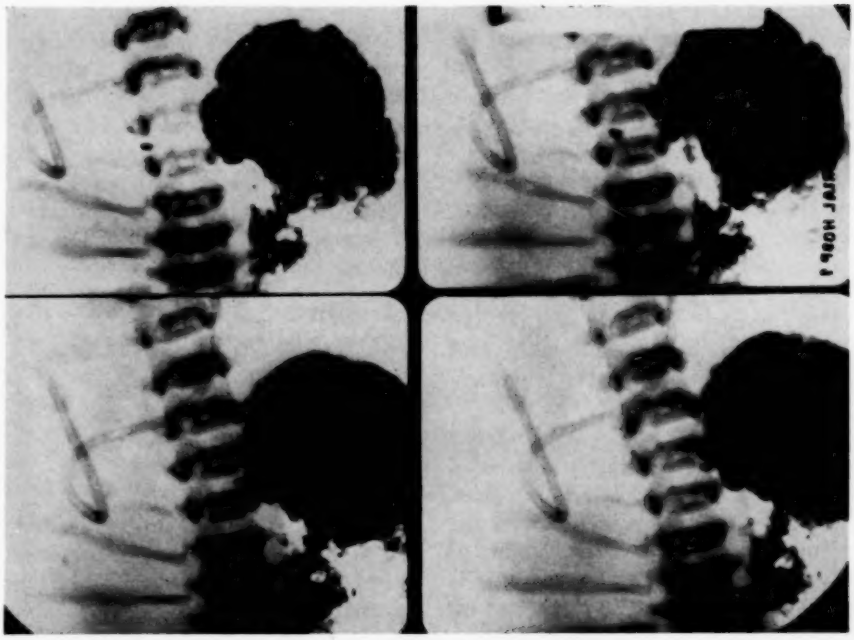

Fig. 2.—X-rays demonstrating almost complete gastric retention following administration of thin barium per gastric tube.

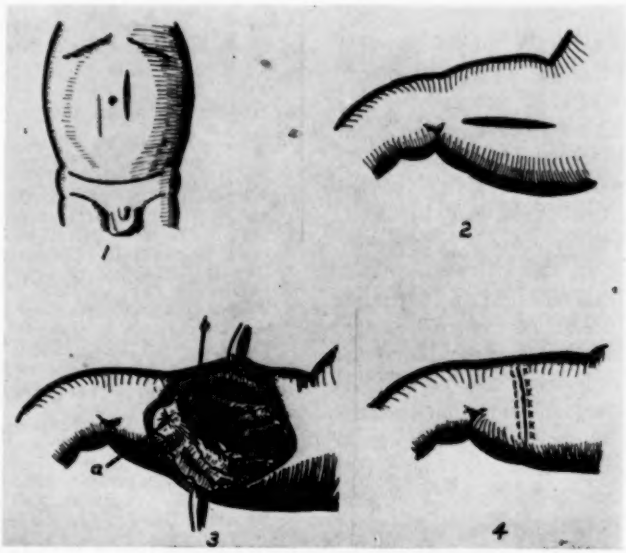

Fig. 3.—Findings and procedure at second operation. *1*, Abdomen showing operative incisions; *2*, longitudinal gastrotomy; *3*, disposition of gastric mucosa: (*a*) central opening in diaphragm, and (*b*) hypertrophic fold of gastric mucosa forming flap valve; *4*, closure of gastrotomy at right angles to initial incision.

Burnett and Halpert[5] reported a case of gastric perforation caused by pyloric atresia and in addition collected two other cases of pyloric atresia without perforation. Bennett[2] reported a case of atresia of the pylorus not associated with meconium peritonitis. A Ramstedt type pyloroplasty was performed, but the infant died within thirty-six hours. Necropsy revealed a lack of continuity of pyloric lumen immediately proximal to the pyloroduodenal junction, which had been uninfluenced by the operative procedure.

Coffey[6] reported a case of atresia of the stomach, likewise unassociated with meconium peritonitis, in which gastrotomy and division of a mucosal diaphragm resulted in alleviation of the obstruction. The present case is considered unique, as it is the first reported case of a valvelike reduplication of gastric mucosa associated with meconium peritonitis with subsequent recovery.

As in this case, the typical physical findings are the following: the infant appears extremely ill, is cyanotic, and dyspneic. The abdomen is distended and there is edema of the abdominal wall and scrotum. X-ray of the abdomen, as first described by Neuhauser,[7] is pathognomonic. Typically the x-ray shows many irregular shadows of calcific density scattered throughout the peritoneal cavity. Pneumoperitoneum may be found, as in this case. Boikan[3] has quoted Litten as noting calcification within twenty-four to forty-eight hours after onset of peritonitis.

The treatment is immediate surgery, in conjunction with proper fluid and electrolyte management. It is suggested here that a small quantity of contrast media administered per gastric tube may indicate some of the possible etiological factors, as previously noted by Brennemann.[4] Its use may demonstrate the underlying obstruction or perforation. If used in this case preoperatively it might have obviated the second surgical procedure. The feeding jejunostomy was an effective temporizing measure until the nature of the obstruction was demonstrated.

SUMMARY

Meconium peritonitis represents a surgical emergency.

The nineteenth case of survival of a patient with meconium peritonitis has been presented. The etiology of meconium peritonitis may vary. The case report of this infant is the first one of perforation due to a valvelike reduplication of gastric mucosa. It is suggested that contrast media be used preoperatively. The value of a feeding jejunostomy should not be overlooked as a temporizing procedure.

We wish to express our appreciation to Dr. Thomas V. Santulli of New York City for his suggestions in preparing this paper.

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VENTRICULAR SEPTAL DEFECT

An Analysis of Twenty-Eight Patients

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ONE of the important congenital cardiac malformations is ventricular septal defect. Until recently no practical method of repair had been perfected. Stimulated by the reports of successful repair by Lillehei and co-workers,[1] we began recommending cardiac catheterization whenever a tentative diagnosis was made, with the object of verifying the diagnosis and evaluating the circulatory changes created by the shunt.

It is now generally recognized that ventricular septal defect is not a benign lesion, and very few patients survive to adult life.[2] Surgical repair is indicated in patients who show evidence of a large shunt or of increasing pulmonary hypertension. Lillehei[3] has shown that the surgical mortality is directly related to the degree of pulmonary vascular change as reflected in the pressures in the pulmonary artery. Because there is no accurate clinical method of measuring the size of the shunt or the degree of pulmonary hypertension cardiac catheterization is a necessary procedure. This paper summarizes the first twenty-eight patients studied at the Raymond Blank Guild Heart Station. No attempt at a statistical analysis is made as the group is not large enough to be definitive but we feel our experience will be found useful.

All patients studied have in addition to a complete history and physical examination x-rays in the posteroanterior and both oblique positions fluoroscopy of the heart complete electrocardiographic studies (in children chest leads V_{4R} through V_6 are included) and previous pertinent records. The electrocardiograms were interpreted independently by two of us (J. G. and H. M.) and differences in interpretation were not significant. The roentgenologist (J. T. M.) recorded his impressions initially and made later interpretations without reference to his previous reports.

Cardiac catheterizations were done without general anesthesia. Premedication was with the shorter-acting barbiturates meperidine and penicillin. Oxygen saturations were obtained with the oximetric method employing both earpiece and cuvette.[4] Pressures were recorded on the Sanborn Poly-Viso Cardiette using the Statham P23D pressure transducer. This technique made it possible in all instances to determine oxygen saturation in the right atrium and right ventricle repeatedly with only a few

From the Raymond Blank Guild Heart Station of Iowa Methodist Hospital and Raymond Blank Memorial Hospital for Children.

seconds between samples. The diagnosis of ventricular septal defect was considered valid with a consistent difference of 5 to 8 per cent. (The figure used is percentage of complete saturation not volume of oxygen per 100 c.c. of blood.) Some of these patients have associated pulmonary stenosis which has been included because the major physiological defect was the left-to-right shunt present in all cases in this series. To date sixteen patients have had surgical repair of ventricular septal defects with two deaths. Seven of these were repaired by Dr. Lillehei at the University of Minnesota with six successful closures and one surgical death. The remaining nine were repaired by Dr. William Myerly at Iowa Methodist Hospital in Des Moines.

The ages of the patients ranged from 4 months to 17 years and there were seventeen males. There was a tendency toward poor growth with most of the patients below average but within normal limits. In all patients a systolic murmur was heard in the left parasternal area maximal from the second to the fourth interspace and associated with a distinct thrill. The patients frequently exhibited some evidence of easy fatigability but it was difficult to separate this from the parents' anxiety. There was definite cyanosis in two patients at times when they had been hospitalized for pneumonia with associated congestive heart failure. There were no other patients with congestive heart failure but there was some tendency toward an increase in the frequency of respiratory infections. In many cases the parents' knowledge of the heart murmur was the chief reason for concern about the child's health.

The patients could be divided into four groups on the basis of catheterization findings:

Group 1	Normal pressure (under 40 mm. Hg)	5 cases
Group 2	Minimal elevation (40-50 mm. Hg)	5 cases
Group 3	Pulmonary hypertension (over 50 mm. Hg)	10 cases
Group 4	With pulmonary stenosis (right ventricle over 50 mm. Hg)	8 cases

The first group include five patients with a normal pressure in the right ventricle and pulmonary artery. While 30 mm. Hg is usually considered the upper limit of normal we have included all patients with pressures under 40 in this group. Our second group consists of five patients with right ventricular pressures between 40 and 50. While this represents definite elevation of the pulmonary artery pressure it is of minimal degree and surgery has not been urged in these cases. Ten patients were found to have pressures in the right ventricle and pulmonary artery over 50 mm. Hg. The figure of 50 was selected because we feel that these patients have or will have pulmonary arteriolar changes. A fourth group includes eight patients with pressures in the right ventricle over 50 but with significant pulmonary stenosis—that is a pressure drop of over 20 mm. from the right ventricle to the pulmonary artery. Surgery has been advised in all patients in Groups 3 and 4.

The following cases illustrate the catheterization findings in each group.

CASE REPORTS

CASE 1.—S. B., is a 3-year-old girl who weighs 28 pounds and is 35

inches tall. She has never been cyanotic. Her parents feel that she tires easily. They have known about her murmur since the first week of life. The essential physical findings include a loud systolic murmur maximal to the left of the sternum with an easily palpated thrill and a clear second sound in the pulmonic area. The electrocardiogram has an incomplete right bundle branch block pattern and left ventricular hypertrophy. The x-rays show enlargement of the heart with displacement of the esophagus and increased pulmonary vascular markings. The heart catheterization gave the following findings:

	Oxygen	*Pressure*
Vena cava	81%	
Right atrium	80%	1
Right ventricle	89%	34/2 mm.Hg
Pulmonary artery	92%	28/14 mm.Hg

While these values indicate a significant left-to-right shunt the absence of pulmonary hypertension indicates that surgery is not urgent and may be deferred.

CASE 2.—R. H. is a 5-year-old girl who has always been asymptomatic. There is no history of cyanosis, failure, or increased respiratory infections. She weighs 47 pounds and is 47 inches tall. The typical thrill and murmur are present. The second pulmonic sound is accentuated. The electrocardiogram is within normal limits. Heart catheterization findings are:

	Oxygen	*Pressure*
Vena cava	78%	
Right atrium	79%	4/0 mm.Hg
Right ventricle	87%	48/0 mm.Hg
Pulmonary artery	86%	32/16 mm.Hg

These findings indicate a moderate left-to-right shunt through a ventricular septal defect with slight increase in pressure in the right ventricle but a normal pressure in the pulmonary artery. These changes are small enough so that surgery does not seem necessary at the present time.

CASE 3.—L. H. is a husky 8-year-old boy who is above average height and weight at 53 inches and 81 pounds. His limitation of exercise tolerance and his exertional dyspnea were minimal but definite. Except for pneumonia in the first year of life, he has never had a serious illness. He has the typical thrill and murmur and the second pulmonic sound is slightly louder than normal. The electrocardiogram shows right ventricular hypertrophy, and the x-rays indicate marked cardiac enlargement with increased pulmonary vascular markings. Cardiac catheterization in January, 1955, gave the following results:

	Oxygen	*Pressure*
Vena cava	54%	
Right atrium	53%	8 mm.Hg
Right ventricle	76%	80/2 mm.Hg
Pulmonary artery	78%	70/32 mm.Hg

Because these findings indicate severe disease, surgery was advised and was successfully performed by Dr. Lillehei in Minneapolis, in November, 1955. The thrill and murmur completely disappeared. The exercise tolerance is now (eight months later) normal and there is no dyspnea. The chest x-ray now shows marked diminution in the size of the heart and in the pulmonary vascular markings.

CASE 4.—R. S. is a 6-year-old Negro boy, who has had nineteen hospital admissions, usually for respiratory tract infections or congestive heart failure or both. His first few months included several severe episodes of failure, but since then the infections have become less severe and less frequent. His weight at one year of age was 15 pounds, and at 6 years was 30 pounds. Cyanosis has not been evident. He has not been able to keep up with other children his size and has dyspnea with exertion. A loud systolic murmur and easily palpated thrill were maximal to the left of the midsternal area, but were heard over the whole chest.

On x-ray, his heart appeared enlarged to the right and left, and the lung markings were increased. The electrocardiogram showed incomplete

right bundle branch block and left ventricular hypertrophy. Cardiac catheterization when he was 4 years of age was as follows:

	Oxygen	*Pressure*
Vena cava	68%	
Right atrium	70%	4/2 mm.Hg
Right ventricle	89%	90/–2 mm.Hg
Pulmonary artery	89%	54/18 mm.Hg

These values indicate a large left-to-right shunt despite the presence of some functional pulmonary stenosis. A 1.5 cm. defect was closed by Dr. Myerly at Iowa Methodist Hospital, in February, 1956. There was no evidence of valvular or infundibular stenosis. The postoperative x-rays demonstrate slight decrease in the size of the heart and the lung markings are within normal limits. His activity is now unlimited and he has gained 3 pounds in the six months since surgery.

ELECTROCARDIOGRAPHIC INTERPRETATIONS

In general, the electrocardiogram reflected the severity of the abnormality, but in each group there were inconsistencies. Of the total twenty-eight patients there were fifteen patients with electrocardiographic evidence of right ventricular hypertrophy, including eight patients with the pattern of incomplete right bundle branch block. There were seven patients with combined right and left ventricular hypertrophy and four of these had an incomplete right bundle branch block. One patient had only left ventricular hypertrophy and five patients had normal electrocardiographic tracings. The electrocardiograms by catheterization groups are given in Table I.

ROENTGENOLOGIC DATA

Interpretation of the x-rays and fluoroscopy was done with special attention to the following: size of the pulmonary artery, vascularity of the lung fields, size of the left atrium, size of the ventricles. No arbitrary standard was used to establish abnormalities because it is our opinion that such criteria are less dependable than the evaluation of an experienced roentgenologist. We also recognized the fact that it is difficult in most instances to differentiate the relative contribution of the right and left ventricles to an abnormal cardiac silhouette.

TABLE I

CATHETERIZATION GROUP	RIGHT VENTRICLE HYPERTROPHY	RIGHT AND LEFT HYPERTROPHY	LEFT VENTRICLE HYPERTROPHY	NORMAL
1	0	1	0	4
2	4	0	0	1
3	6	4	0	0
4	7	0	1	0

There was only one patient who had x-ray findings within normal limits. This was a 17-year-old girl who was asymptomatic, with a normal electrocardiogram and catheterization evidence of a small shunt without pulmonary hypertension. Pulmonary vascular markings were increased in the great majority of patients. Prominence of the pulmonary artery was a common finding. The right ventricle appeared larger than normal in all of the x-rays although in six cases this was minimal. In every example of marked enlargement the right ventricular pressure was elevated and there was either pulmonary artery hypertension or evidence of stenosis of the pulmonary valve. However, the converse was not true. There were some patients with marked pulmonary hypertension who did not have comparable x-ray findings.

SURGICAL RESULTS

Of the twenty-eight cases in this series, surgery has been recommended for seventeen. One patient died during cardiac catheterization. The results by catheterization groups are given in Table II. One patient for

TABLE II

CATHETERIZATION GROUP	NO. CASES	NO. OPERATED UPON	NO. SUCCESSFUL
1	5	0	
2	5	0	
3	10	8	7
4	8	8	7
Total	28	16	14

whom surgery has been recommended has not been seen again. Seven of the operations were at the University of Minnesota; there was one death in this group. The other nine were at the Iowa Methodist Hospital in Des Moines, with one death. Of the postoperative patients, four still have significant murmurs. Two of these are children who had an infundibular stenosis removed at surgery and still have palpable thrills and loud murmurs. Another is a 5-year-old boy who had fibroelastosis demonstrated at the time of surgery and has a loud apical systolic murmur. It is thought that he may have a mitral insufficiency (caused by the fibroelastosis) as the cause of this murmur. All three of these patients have had considerable improvement over their preoperative status in terms of exercise tolerance. The fourth patient had a large moderator band which had to be removed in order to get at the defect, and she still has a loud systolic murmur. Cardiac catheterization will be repeated on these patients.

DISCUSSION

This is a review of an unselected group of patients. We have advised cardiac catheterization whenever the tentative diagnosis was ventricular septal defect. It is apparent that in this group the shunt of blood from left to right through the defect was great enough to alter the hemodynamics measurably. The pressures in the right ventricle were elevated, often to a marked degree; the right ventricle was enlarged in all except one and the left ventricle in some; there were signs of increased flow of blood to the lungs; and there was evidence of poor growth. Five patients studied had small enough defects to leave the right side of the heart apparently undisturbed and three of these were in young patients (4, 5, and 5 years old) whose x-ray and electrocardiographic findings leave room for doubt that their catheterization findings will remain normal. We wish to emphasize the fact that many of these patients were brought in for examination because they had heart murmurs and few symptoms.

We have found it impossible to predict accurately the physiological disturbance by clinical means. Symptoms, physical signs, x-rays, and electrocardiograms were not consistently abnormal in relation to each other or in relation to the size of shunt or elevation of pulmonary artery pressure. Perhaps with greater experience some correlation will be found. It is interesting that no patient with right ventricular pressures over 50 mm. Hg had a normal electrocardiogram.

There is an apparent disagreement between x-ray and electrocardiographic evidence of chamber enlargement. This probably represents to

some extent a means of distinguishing between hypertrophy of the wall and dilatation of the ventricle. The right ventricle ejects the normal venous return plus an additional amount shunted into it from the left ventricle. There is probably a prolonged ejection phase. When pulmonary hypertension is present the increased resistance to the flow of blood causes the right ventricle to work even harder. In time this produces hypertrophy of the overworked myocardium. The time of onset and degree of hypertrophy are directly related to the size of the shunt and the elevation of pulmonary artery pressure. Eventually the hypertrophy may be reflected in the electrocardiogram. Hypertrophy and dilatation may cause similar changes in the x-ray appearance of the heart. The left ventricle is also forced to do extra work but to a different degree. The additional amount of blood ejected from the right ventricle is returned to the left ventricle, causing greater diastolic filling (and, incidentally, contributing to the left atrial enlargement frequently seen). If the distention which occurs during this time is great enough there is a significant dilatation of the ventricle. During systole there is a relatively low peripheral resistance since there is no arterial hypertension and there is a rapid run-off of blood being shunted through the septal defect. As a result the work of the left ventricle may be increased only slightly and not enough to produce hypertrophy which is detected in the electrocardiogram. The dilatation of the chamber, however, may be great enough to be recognizable by x-ray, thus accounting for an apparent inconsistency in clinical findings.

Because the surgical mortality in those cases without severe pulmonary hypertension is quite satisfactory, we are recommending surgery for all patients with a pulmonary artery or right ventricular pressure over 50 mm. Hg. As with patent ductus arteriosus, a reversal of shunt with cyanosis greatly decreases the chance for corrective surgery and in some cases is a contraindication for surgery.

SUMMARY

The first twenty-eight patients with ventricular septal defect proved by cardiac catheterization have been summarized. The patients were children, with no special selection other than the diagnosis made clinically. The lesion usually was associated with electrocardiographic and roentgenologic abnormalities and with significantly elevated pressures in the right ventricle and pulmonary artery. We consider ventricular septal defect an abnormality which is serious enough in most instances to justify surgical repair with the least possible delay. Of twenty-eight patients sixteen have had surgery with fourteen successful repairs.

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HARLEQUIN COLOR CHANGE IN A YOUNG INFANT WITH TRICUSPID ATRESIA

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IN 1952 Neligan and Strang[1] described an unusual cutaneous phenomenon in newborn infants which they called the harlequin color change. This phenomenon is observed occasionally in newborn and premature nurseries, occurring in 9 per cent of premature infants cited in the original report. The phenomenon consists of episodes during which a sharp midline change in skin color occurs. A precise line of demarcation bisects the body into pale and plethoric halves. This occurs when the infant is turned upon his side. The dependent half of the body becomes suffused, and the upper becomes pale. No permanent or pathologic findings persist in infants who show this phenomenon in the neonatal period.

The precise midline distribution of this color change makes it likely that the condition is mediated through the suprasegmental autonomic centers of the hypothalamus where the tone of the cutaneous blood vessels is controlled.[2] Herlitz[3] has demonstrated that this vasomotor control is unilateral.

A recent American report[4] describes a term infant with the phenomenon, but it is probably more frequently observed in premature than in term infants. However, the common practice of placing premature babies, relatively unclothed, in transparent incubators and observing them continuously may account for this seemingly increased incidence.

The condition is most frequently seen during the third and fourth days of life. Neligan and Strang[1] observed an infant with the color change at 21 days of age and Herlitz[3] noted it in a 28-day-old baby. There are no reports of this phenomenon in older infants.

This paper describes an infant with cyanotic heart disease who demonstrated the harlequin color change during the first three and one-half months of his life. At this time an aorta to pulmonary artery anastomosis was successfully performed. The child was not clinically cyanotic after operation and the phenomenon was no longer observed.

CASE REPORT

History.—M. R., a 6-pound 14-ounce white male, was born of an uncomplicated monozygotic twin pregnancy. Monozygosity was determined by the finding of a single chorionic membrane. The patient was the firstborn and cyanosis and a heart murmur were noted shortly after birth. The identical twin was entirely normal.

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The opinions or assertions contained in this article are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

The child was taken home at 7 days of age; he did fairly well until he was 2 months old, when he was admitted to another hospital because of dyspnea and apnea. Despite constant oxygen administration, the spells of apnea became more frequent and protracted. At 3 ½ months of age he was transferred to the United States Naval Hospital, Bethesda, Maryland.

Physical Findings.—The infant was small and moderately cyanotic and early digital clubbing was present. His weight was 7 pounds 12 ounces. A soft systolic murmur was heard over the precordium. The second heart sound over the pulmonic area was not split. The liver edge was palpable and did not pulsate.

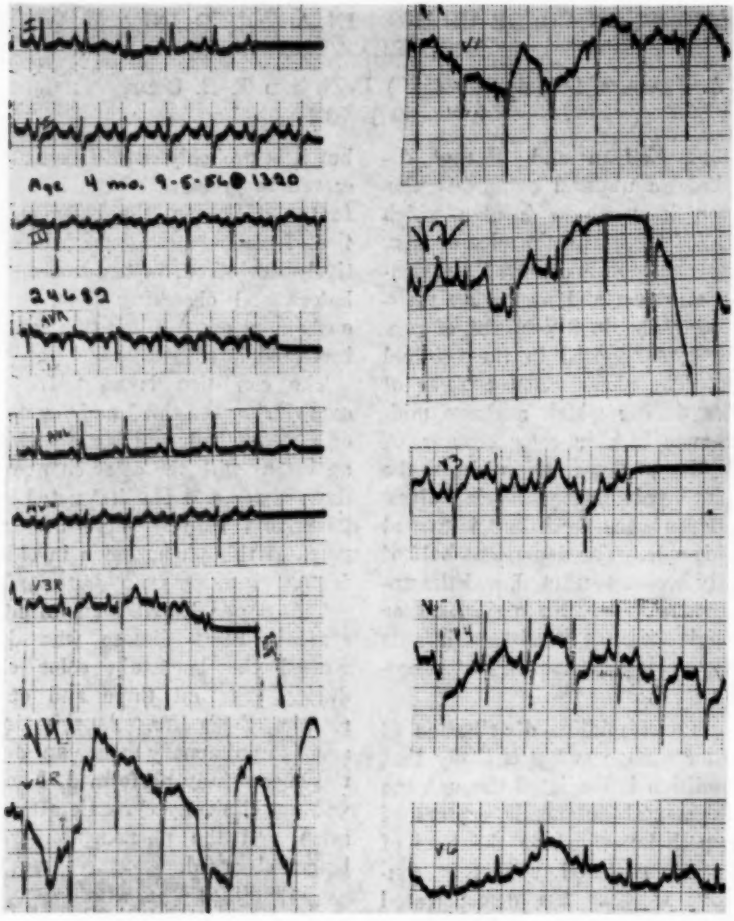

Fig. 1.—Electrocardiogram demonstrating left axis deviation and left ventricular hypertrophy.

Laboratory Findings.—The hemoglobin was 18.0 grams per cent. Roentgenogram of the chest showed hypovascular lung fields, a concave pulmonary artery segment, and probable

left ventricular enlargement. An electrocardiogram demonstrated left axis deviation and left ventricular hypertrophy (Fig. 1). Accordingly, the diagnosis of tricuspid atresia was made.

Shortly after admission it was noted that the child was demonstrating the harlequin color change. When placed on either side, a gradual suffusion of the dependent side occurred. There was an acute line of demarcation, exactly at the midline, running from the forehead through the chest and navel to the pubic symphysis and including the penis and scrotum. The dependent arm and leg were suffused, the back was also bisected. The color change would remain for ten to twenty minutes and then fade. The color change could also be reversed by reversing the dependent side. During the episodes of color change no difference in the size of the pupils or irregularity of body temperature occurred.

The parents stated that they had noticed a unilateral color difference on the child's face and body when he was 8 days old. This was noted on many occasions while the baby was at home and after he had entered the other hospital. The normal twin never demonstrated the harlequin phenomenon.

When the child was recumbent the skin was of a pale, slightly cyanotic hue. When he was turned the upper half remained the same color while the dependent side became more red. This would indicate that dependent vasodilatation was the mechanism for the change.

The color change was observed nearly continuously during four days of hospitalization. On the morning of the fifth hospital day the color change was observed, and shortly after this the child was taken to the operating room. A side-to-side anastomosis between the aorta and the left pulmonary artery was performed through a left thoracotomy incision. After surgery the child was no longer clinically cyanotic. Despite frequent changes in position, the harlequin phenomenon was not seen again.

The child did well on the first three postoperative days. However, on the fourth day he developed fever and rapid respirations. Despite antibiotics, digitalis, and mercurial diuretics the child did not respond and died quietly on the morning of the fifth postoperative day.

Necropsy Findings. — Post-mortem examination which was confined to the thorax showed atresia of the tricuspid valve, diminutive right ventricle, a small interventricular septal defect, and a patent foramen ovale. The operative shunt was patent. A diffuse bronchopneumonia and necrotizing pleuritis was present; culture of the pleural exudate grew out a hemolytic, coagulase-positive staphylococcus.

SUMMARY AND CONCLUSIONS

The harlequin color phenomenon is a midline demarcation of the body into pale and plethoric halves. This is seen in the neonatal period, and is probably more frequent in premature infants. It is thought to be due to a transient vasospastic phenomenon in the hypothalamus where there is unilateral control of the tone of the cutaneous blood vessels.

The present report describes a 3½-month-old child with cyanotic heart disease, proved at autopsy to be tricuspid atresia. During his life the child was observed to demonstrate the harlequin phenomenon. Vasodilatation of the cutaneous blood vessels of the dependent half of the body was the mechanism for the change in this infant. After the clinical cyanosis was corrected by an aorta-pulmonary artery anastomosis, the color change was no longer observed. The cessation of the condition after the relief of the

cyanosis by operative intervention might be coincidental. It is more likely, however, that arterial oxygen unsaturation was of importance in the production of the harlequin phenomenon in this child. Since cyanosis is frequent during the neonatal period, especially in premature infants, anoxia may be a triggering mechanism for this condition.

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An Enquiry Into the Nature, Cause, and Cure, of the Angina Suffocativa, &C.

I have had an opportunity of examining the nature and seat of this disease, from dissection, in three instances. One was a child of three years old. Her first complaint was uneasiness in her throat. Upon examining it, the tonsils appeared swelled and inflamed, with large white sloughs upon them, the edges of which were remarkably more red than the other parts of the throat. She had no great soreness in her throat, and could swallow with little or no difficulty. She complained of a pain under her left breast; her pulse was quick, soft and fluttering. The heat of her body was not very great, and her skin was moist; her face was swelled, she had a considerable prostration of strength, with a very great difficulty of breathing, a very remarkable hollow cough, and a peculiar change in the tone of her voice. The next day, her difficulty of breathing was increased, and she drew her breath in the manner before described, as if the air was forced through too narrow a passage, so that she seemed incapable of filling her lungs: She was exceedingly restless, tossing perpetually from side to side, was sensible, and when asked a question, would give a pertinent answer, but otherways she appeared dull and comatous. All these symptoms continued, or rather increased, until the third night, on which she had five or six loose stools, and died early in the morning.

Upon examining the body, which was done on the afternoon of the day she died, all the back parts of the throat, and the roof of the tongue were found interspersed with sloughs, which still retained their whitish colour. Upon removing them, the parts underneath appeared rather pale than inflamed. No putrid smell could be perceived from them, nor was the corps in the least offensive. The Oesophagus, *or gullet*, appeared as in a sound state. The epiglottis, *which covers the wind-pipe*, was a little inflamed, on its external surface, and on the inner side, together with the whole larynx, was covered with the same tough white sloughs, as the glands of the throat. The whole trachea quite down to its division in the lungs, was lined with an inspissated mucus, in form of a membrane, remarkably tough and firm; which, when it came into the lungs, seemed to grow thin and disappear: It was so tough as to require no inconsiderable force to tear it, and came out whole from the trachea, which it left with much ease; and resembled more than any thing, both in thickness and appearance, a sheath of thin shammoy leather.

SAMUEL BARD, 1771.

THE DEVELOPMENT OF SEX-ROLE INVERSION AND HOMOSEXUALITY

DANIEL G. BROWN, PH.D.
DENVER, COLO.

A NECESSARY DISTINCTION

MANY workers who have concerned themselves with the problem of sexual deviation have failed to distinguish between homosexuality and sexual inversion, or, more accurately, sex-role inversion. Jenkins[13] makes a special point of this differentiation as follows: "We are speaking of sexual inversion, which is not identical with homosexuality. While inverts are commonly homosexuals, not all homosexuals are inverts. There are certain very masculine male homosexuals . . . who find as their sexual partners younger, softer and more feminine men. The latter may be inverts, the former are not."

Freud[1] completely equated the two terms as follows: "It is, therefore, very surprising to find that there are men for whom the sexual object is not woman but man, and that there are women for whom it is not man but woman. Such persons are designated as contrary sexuals, or better, *inverts*, and the situation of such a relationship is called *inversion*."

The impact of Freud's thinking is reflected in the definition of inversion in the *Psychiatric Dictionary*[12]: "The expression sexual inversion is used today in psychiatry in its psychoanalytic sense. . . . the term *invert*, usually modified by sexual, is synonymous with homosexualist." The *American Illustrated Medical Dictionary*[7] also follows this practice in defining the invert as "a person whose sexual interests and impulses are directed toward a person of the same sex," and inversion as ". . . homosexuality." Many other authorities use the terms synonymously: Thorpe and Katz,[24] Coleman,[6] Henderson and Gillespie,[10] Caprio,[5] and Sappenfield.[22] For these writers, no distinction is made or even implied, that is, an invert is a homosexual and a homosexual is an invert. The *Dictionary of Psychology*[25] lists two separate definitions of inversion, one of which follows the conception to be emphasized in the present paper; the other is listed as a "psychoanalytic" definition in which inversion is simply equated with homosexuality.

In contrast to the practice of using the two terms as equivalents, some writers have specifically pointed to the need for differentiating between inversion and homosexuality.[8, 13, 16, 17, 26] Ferenczi,[8] as early as 1911, recognized the essential difference between inversion and homosexuality in his discussion of "two types" of homosexuality. Morgan and Lovell[17] define sexual inversion as the process in

From the Department of Psychology, United States Air Force Academy.

cyanosis by operative intervention might be coincidental. It is more likely, however, that arterial oxygen unsaturation was of importance in the production of the harlequin phenomenon in this child. Since cyanosis is frequent during the neonatal period, especially in premature infants, anoxia may be a triggering mechanism for this condition.

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which a person of one sex takes on the characteristics of the other sex. However, in their glossary, these same writers define the invert as a "homosexual."

Although White[26] does not use the term inversion, he nevertheless mentions the fact that homosexuality "includes two rather different kinds of deviation":

"The disorder may be strictly limited to the choice of object. In so-called active male homosexuality and passive female homosexuality the individual takes a role entirely appropriate to his sex, stipulating only that the partner shall be of the same sex. The situation is different with passive male homosexuals ('fairies') and active female homosexuals ('Lesbians'). Here the role appropriate to the opposite sex is desired."

Lindesmith and Strauss[16] make a clear, straightforward distinction in pointing out that inversion involves the assumption of a female role by a male and of a male role by a female.

The above review of the usage in professional thinking and literature of the terms inversion and homosexuality suggests considerable variation among writers. A major thesis of the present paper is that the loose use of homosexuality and inversion as synonymous and the failure to make clear the difference between them has resulted in conceptual confusion and has hindered the attempt to understand both the nature of sex-role inversion as well as the psychodynamics of homosexuality. The purpose of this paper is to stress the need for a definitive clarification and to point out some important developmental implications.

In basic agreement with those who sharply differentiate between these phenomena, the following distinction is offered: *homosexuality* refers to sexual activity or the desire for such activity between two members of the same sex, whereas *sexual inversion* refers to the identification with and adoption of the psychological identity of the opposite sex. The basis for the development of inversion appears to be a primal and pervasive identification-attachment to the parent of the opposite sex.* Such identification probably occurs on an unconscious or involuntary basis in the earliest years of life and appears to be the kind of learning that Mowrer[18] refers to as conditioning or "emotional" learning. Later, as the child matures, he gradually comes to accept on a *conscious* basis the sex role patterned after the parent of the opposite sex and perceives this role as an integral part of himself.[2]

The homosexual, then, is one who desires and/or obtains predominant or exclusive sexual satisfaction with members of his own sex. The invert is one whose thoughts, perceptions, attitudes, fantasies, feelings, preferences, interests, and behavioral tendencies are typical of the opposite sex.[2] Homosexuality is quite restricted in meaning, referring simply to an individual's aim and object in sexual activity per se, while inversion is a much broader phenomenon, referring to the composition of the individual's total personality structure and not merely his preferred form or mode of

*The idea that a strong, close attachment in childhood to the parent of the *same* sex is also conducive to the development of homosexuality in adulthood has been criticized by Mowrer[20] who writes: ". . . one may reasonably doubt that any little boy ever became a homosexual because he had 'once been fond of his father.' In fact, a strong affectional bond between son and father appears to be the best possible insurance of like-sex identification and normal heterosexuality."

sexual activity. In a very real sense the typical invert may be described as a psychosomatic misfit in that his body is characteristic of one sex (e.g., anatomically male) but his personality is characteristic of the other sex (e.g., psychologically female).

It might be predicted that an individual whose sex role is inverted would seek a love object of the same biological sex, that is, be predisposed to perversion in the form of homosexuality.[11, 23] Thus, the passive male homosexual and the active female homosexual are individuals whose sexual behavior is to be understood as an outgrowth or expression of their over-all inversion; the male invert psychologically perceives himself as a female, and accordingly looks to the "opposite" sex for sexual gratification. In this connection the writer recalls a clinical staff conference in which the case presented was that of a male invert who, when interviewed, was asked if he had ever engaged in homosexual behavior. He replied in the negative. Later, during the same interview, when asked if he had ever had sexual relations with a man, replied, "Oh, yes, many times." This man obviously did not feel that there was any contradiction in his answers since he perceived himself as a female, and his sexual activity with males was for him heterosexual, *not* homosexual!

The fact that certain forms of homosexuality (male passive and female active) seem to develop as an outgrowth of inversion does not mean that all homosexuality has its origin within this context. There is considerable evidence that suggests a number of other correlates and predisposing conditions (social, psychological, and biogenetic) that are functionally related to the development of homosexuality.[11] This is another reason for distinguishing it from inversion.

It can be seen from the above discussion that inversion is not the same as homosexuality, and, although the inversion of an individual's personality will most likely involve homosexuality, not all homosexuality is based on an inversion of personality. It is fallacious to use one term to refer to the other. Perhaps it would not be incorrect to say that about all that many homosexuals have in common is their preference for sexual activity with members of the same sex, and it might be predicted that the inverted homosexual is fundamentally different in personality structure from the noninverted homosexual.[23] If this prediction is confirmed, the failure of most attempts to distinguish between "homosexuals" and normal subjects on the basis of psychometric data becomes quite understandable. The criterion in most investigations of this type for classifying a subject as "homosexual" is simply a history of predominant or exclusive sexual activity with the same sex. The fact that no distinction is made between inverted and noninverted homosexuals is most likely a major reason for the uniformly poor discriminations reported by such studies.

SEX DIFFERENCES IN INVERSION

One interesting question related to the present discussion is whether or not the incidence of inversion differs in males and females. Mowrer, in a personal communication to the writer, raised this question in connection with a study of sex-role preference

patterns in children[2] which, among other things, provides information on differences in the acceptance of sex roles and on preferences for the role of the opposite sex in boys compared to girls.[2] The Kinsey studies[14, 15] show a greater frequency of homosexuality among males. Although this finding does not necessarily mean that inversion is also more common among males, the theoretical views of Parsons,[20, 21] Gorer,[9] Mowrer,[18] Sears,[2] and others would make plausible such an assumption. The basis for predicting greater frequency of inversion in males than in females would be as follows: Boys as well as girls form an initial identification with the mother (feminine model); in the case of boys, however, a shift in identification must be made to the father (masculine model) if normal sex-role development is to occur; girls are not faced with this shift since they start out with an identification with the mother and, as long as there is a reasonably healthy relationship with the mother or mother-surrogate, girls simply continue the process of feminine identification (one aspect of which later is a love object-choice of the opposite sex, hence a turning to the father as the first such choice and, later, eventuating at maturity in the desire and choice for a mate of the opposite sex). Despite the Freudian emphasis on the anatomical difference between males and females or the Adlerian emphasis on discriminations against females in the sociocultural environment and the denial of equal freedom and prerogatives with males, a satisfactory mother-daughter relationship makes it possible for the little girl, both consciously and unconsciously, to incorporate the feminine role. Even though she may "envy the anatomical advantage of the male," even though there is a "masculine protest" on her part, and even though she may find the masculine role more attractive, the fact remains that she has basically introjected the feminine role. Hence, inversion would be expected to develop only in cases where there is a serious disruption in the mother-daughter relationship that prevents the little girl from identifying with the mother or where the mother herself denies or despises her own femininity and thus exposes the daughter to a distorted feminine model.

The little boy, however, is initially and often continually exposed to the female role exemplified by the mother; the original identification of practically all males is with the feminine model. If in these early, formative years the father is physically absent and there is no adequate substitute, or the father is weak and ineffective in relation to a dominant and aggressive wife, or the father is cruel, excessively harsh, or indifferent to the needs of the boy, or the father is more or less a psychological nonentity for the boy—if these or similar conditions exist, together with an early, excessively close and unusually strong identification-attachment with the mother, the result is a failure to incorporate the masculine role. No matter how much the culture itself may seem to favor the male role, such a boy has made a basic identification with the feminine role and early begins to show a preference for this role.

It might be added here that boys, in contrast to girls, are not likely to

prefer the role of the opposite sex unless they have incorporated that role through identification with the feminine model. The reason for this is the fact that the cultural pattern is more favorable to the male than to the female. In other words, a boy who shows a preference for the feminine role is in all probability one who has also *identified* with that role, the result of which is inversion. Specifically, such a boy typically prefers dolls, likes household activities such as cooking and sewing to the exclusion of activities typical of boys, wants to dress, talk, and look like a girl, and, not uncommonly, somehow expects to be changed into a girl.[11, 23] It is this development that constitutes inversion.

The same does not follow in the case of the girl who, although preferring the masculine role (and evidence indicates many girls do prefer much that is associated with masculinity[3]) she has *not* necessarily identified with that role. The development of inversion in females would seem to depend on both a basic and predominant identification with and preference for the masculine role. In any event, this discussion serves to provide a partial basis for understanding how it is possible that the percentage of girls who show a preference for the masculine role may be considerably higher than the percentage of boys who show a preference for the feminine role, yet the incidence of homosexuality be considerably higher in males than in females. In light of the same discussion, it may be hypothesized that sex-role inversion is more common in males than in females.

DIFFERENCES IN STABILITY OF SEX-ROLE DEVELOPMENT

Another implication of the present paper has to do with the assumption of a difference between males and females in consistency and continuity of sex-role preference from childhood to adolescence and adulthood. Observations and some additional research data obtained by the writer[3] suggest that boys are much more constant and less variable in sex-role preference development than girls.

In a study* of masculinity-femininity preference in children from kindergarten through the fifth grade (age range from about 5½ to 11½ years), a preponderance of boys in each age group shows an overwhelming preference for aspects of the masculine rather than the feminine role, whereas girls, *with the exception* of those in the fifth grade, are quite heterogeneous, some showing a greater preference for feminine aspects but the majority showing a predominant preference for masculine alternatives.

Many girls then appear to reach the stage of puberty with a background characterized by "tomboyishness," masculine strivings of various kinds, and other manifestations suggesting a strong preference for the male role, that is, inverted tendencies. However, with the onset of pubescence and the beginning of physiological maturity, most of these same girls discard their masculine preferences and masculine ways and become thoroughly feminine in interests and

*This study is based on the use of a sex-role preference scale known as *The It Scale for Children*.[4] The scale provides a basis for evaluating masculinity-femininity patterns in children, a problem which Terman and Miles[23] recognized many years ago when they stressed the need for such a test.

behavior. In the case of boys, however, those who enter pubescence with a background of "girlishness" and feminine tendencies seem to retain such an inverted pattern which, in fact, seems to become more intense and fixed.[23] The question is: Why this difference between such males and females?

The above discussion would appear applicable here in the following way: The *role identification* (i.e., the introjection of the psychological identity of one sex in contrast to the other sex) of these girls is and always has been basically feminine although their *role preference* (i.e., the overt, sex-typed behavior that is perceived as most desirable) has been somewhat or even predominantly masculine.[2] With the added impetus of physiological changes in puberty and psychological changes in adolescence, together with thoughts of approaching marriage and eventual motherhood, they tend to become more feminine and their previous idolization of masculinity declines sharply. The role identification of such boys, on the other hand, is and probably always has been basically feminine, and, together with an obvious preference for the feminine role, continues to be expressed and gives rise to the adolescent and adult male invert. In short, opposite sex-role *identification plus* opposite sex-role *preference* appear to lead to the development of inversion, while *preference without identification* does not. And it might be hypothesized that *identification without preference* leads to a conflictual, ambivalent, confused, and unstable personality structure in which the individual does not perceive himself clearly in either role.

SUMMARY

The importance of differentiating between sex-role inversion and homosexuality is emphasized. Inversion refers to the adoption of the sex role and introjection of the psychological identity of the opposite sex. Homosexuality refers to sexual desire and activity between two members of the same sex. Thus, while certain forms of homosexuality (passive male and active female) are expressions of personality inversion, other forms of homosexuality have nothing to do with inversion. Failure to observe this basic distinction results in confusion, both in theory and research.

It is hypothesized that inversion has its roots in the earliest years of life when the child forms, at first involuntarily and later consciously, an identification-attachment to the parent of the opposite sex and thereby introjects the sex role of the opposite sex. The invert, then, is a psychosomatic misfit, having the body of one sex and the personality of the other sex.

Though more girls than boys express a preference for the role of the opposite sex, the possibility that inversion, as well as homosexuality, is more common in males than in females is discussed in terms of developmental personality theory. Also discussed is the basic difference between the sexes in relation to the meaning of expressed preference for the sex role of the opposite sex. In this connection it is necessary to distinguish between sex-role identification and sex-role preference.

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CHILD CARE IN IRAN

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IRAN is a vast country whose habits and way of life reach back to the dawn of history. It is a land of striking contrasts, a land deeply influenced by religious attitudes and climatic differences. Here populations can be found which illustrate the successive changes in the history of human beings. At one end of the scale are the nomad tribes of the south who are constantly on the move, traveling as much as 600 kilometers each year, northward or southward depending on the season. They carry on a primitive existence, moving by camel or donkey, living together with their animals, and spinning their own wool.

At the other end of the scale are the people in the large cities. They enjoy most of the privileges of modern life and even overdo it sometimes. They bring up their children according to western ideas. Then there is the intelligentsia who are educated but not necessarily rich. Since they are well acquainted with modern methods of child-rearing, their way of life and their child-care attitudes would not be of much interest to the reader. This class, consisting principally of government employees and employees of big firms, is growing rapidly. It is restricted to the large cities.

It seemed wise to devote this article to the care of babies in our third, fourth, and fifth classes: the people in small towns, the peasants, and the tribes people. Their ways do not differ greatly from one another but, where it does (as between nomads and peasants), I will mention it. I hope my frankness and precision, which do not allow me to overlook certain unpleasant facts and sights, will not offend any of my compatriots who may happen to read this article.

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MORTALITY

The population of Iran is estimated to be about 18 million. In the south about one million lead a tribal existence. They, as well as the peasant class, marry early. If they can afford a wife, they marry when they are 16 or 17 years of age. Persian law does not permit marriage of girls younger than 15 years, but still some girls marry at an earlier age. Birth control is unknown. The birth rate is very high (a young couple would have a baby every year or so), but so is the death rate. According to figures which I have collected, it is as high as 22.2 per cent during infancy, and is probably even higher in the hot coastal areas. A woman of 40 usually has from one to three children, but if you ask her how many babies she gave birth to, the figure would certainly be over ten. About 3 per cent of the infant mortality occurs in the first twenty-four hours of life, 17 per cent

in the neonatal period, and 48 per cent in the first year of life. These figures relate to the poor people of the towns where free prenatal and postnatal care is available.

As to the causes of this high mortality, the infectious fevers and summer diarrhea come first; not far behind are starvation, malnutrition, and faulty techniques of feeding. At later ages rheumatic fever, infections, particularly diphtheria, whooping cough, nephritis, typhoid fever, malaria, and accidents, play a big role. The accidents are principally burns, falling into pools or wells, and falling from the roof during summertime, while sleeping there to get the cool breeze of night. A few years ago, when opium smoking was still prevalent, more than two cases per week of opium poisoning in infants were encountered in a busy private clinic. In most of these cases the ignorant mother intended to quiet the crying baby with what she called "ecstasy pills." Instances were seen where a toddler put pieces of chocolate-looking opium in his mouth and swallowed it. When Dr. J. Saleh of Syracuse University in New York became Minister of Health, he started an intensive campaign against opium and now no cases are in existence.

Smallpox is no longer a major cause of death as the most ignorant peasant or nomad welcomes vaccination. This is the only popular prophylactic measure eagerly accepted by them. Tetanus is seen occasionally. Protective inoculation has not been enforced in rural areas. Congenital syphilis is becoming rarer since penicillin was introduced.

Fig. 1.—Tribe on the move. Donkeys and camels are loaded with the belongings of the family. Sometimes, for a few hours, babies, old lambs, chickens, or hens are put on top of the load. Sheep and goats follow in the rear.

Twins are no fewer than in Western countries, but they rarely survive the hazards of infection and malnutrition. Almost all premature babies die. Percentagewise it is not a prominent cause of death in infants.

BIRTH AND NEWBORN PERIOD

Prenatal and postnatal clinics have been opened during the last ten years

Fig. 2.—A mother with a baby on her back, a newborn lamb in one hand, and a big stick in the other chasing the animals.

Fig. 3.—Mother carrying the baby on her back.

in most of the big cities. Trained midwives have been sent by the government to some small towns or villages, but the majority of deliveries are still conducted by lay midwives and other ignorant women who do not know much about it. In villages and among the tribes the older, more experienced women help the younger ones. Most of the time labor is performed in the sitting position, usually over a "U"-shaped hearth. The cord is dressed with burned cotton wool or a rag.

A nomad woman does not fuss very much about her labor. As soon as the labor pains begin, the family and all its animals halt their journey. This interruption does not last very long; they usually continue their travel after a few hours and soon catch up

Fig. 4.—While working, cleaning wheat in this instance, the mothers do not leave their babies. This is in front of a typical village.

Fig. 5.—Children playing outside the village walls. The 6- and 7-year-olds look after the babies.

with the other part of the moving tribe. But this time the nursing woman does not run after sheep or goats; she would rather ride a camel. Most of the difficult deliveries end in catastrophes.

Boys are appreciated much more than girls. Up to twenty years ago, the chieftains of a tribe turned over the girls to be brought up by servants for the first few years. "Daughter enough" is a rather common name for a girl in Iran. That means that a family had too many daughters and no sons. Under the magic spell of the new name "Daughter enough" the next pregnancy is supposed to produce a boy.

The first forty days of life have a special significance. Mothers avoid taking the child out except under dire necessity. This naturally does not apply to the tribes people. In towns the women say for example: "The child is ill since a week, but I was waiting for his '40' to be over." It shows that these people appreciate the diverse problems and difficulties of the neonatal period.

The mean birth weight is over 3 kilograms (3.32 kilograms for boys and 3.27 kilograms for girls, according to my data). Mothers swaddle their babies very tight and straight. They believe that if the baby is not wrapped in this way for the better part of infancy, he will get "crooked legs." Swaddling (Fig. 6) is done with three to ten sheetlike pieces of material. The first one or two layers are of soft material and go between the legs as well. The legs are kept very straight during swaddling. After the first and second sheet come oilcloth or rubber sheets, then a few more layers which keep the baby's arms close to its body. The baby is unable to move his arms or legs. Finally he is put in a bigger sheet and tied to his mother's back, where he will not interfere with her daily work.

Fig. 6.—Baby in swaddling clothes.

The mothers are very fond of their children and scarcely ever leave them. They carry them on their backs while they are washing, milking animals, baking bread, or carrying something (mostly washed potteries) on their heads. In towns a cord is tied around the last swaddling sheet.

All boys are circumcised. This usually takes place during the first month, but it is sometimes postponed for several years. In well-to-do families living in big villages and towns, it is an occasion for a celebration. The operation is usually performed with a razor blade or knife, mostly by Jewish people.

FEEDING

Breast feeding is the rule. In small towns dried milk has been introduced, but it has done more harm than good. This is because highly diluted mixtures (1:20 or 1:30) are used as the result of wrong instructions, or to save money, or for fear of summer diarrhea. Underweight and even marasmic babies are common results of such faulty feeding.

Fig. 7.—Malnutrition. Administration of rose water instead of milk was the cause of this condition. The baby was 9 months of age and weighed only 2,900 kilograms.

Unfortunately, this cause has not been fully appreciated by people who look after these poor babies or treat them. The babies frequently become sick, whereupon rose water or almond oil is administered. The vicious circle continues. I have seen 15- or 16-month-old babies weighing only 3 kilograms or even less.

Breast feeding is continued for two years or more. It is generally believed that girls should be breast fed for twenty-four months and boys for twenty-two months. If one questions this discrimination, one is told that, according to the Mohammedan religion, the girls of a family inherit half as much as boys; in other words, two girls inherit as much as one boy. Therefore, to make up for this deprivation, the girls are nursed longer. It is difficult to convince mothers that prolonged nursing is not a favor to the baby. I usually appeal to their religious sense and prejudices. I tell them that the teeth are for chewing and for dealing with harder food; and, as the teeth begin to erupt at 6 or 7 months of age, this should be considered as an indication for new food in the baby's diet. This kind of reasoning works most of the time.

In the second year of life different kinds of food, mostly rice, soup, and bread, are introduced to the baby's diet, but breast feeding is continued. In the tribal area one often sees a toddler of 2½ or 3 years running to his mother, taking the breast out of her wide open dress, and starting to please himself. As a matter of fact, "putting the breast in baby's mouth" is the usual way to quiet the youngster.

There are no special feeding times. The breast is given whenever the baby cries, although the cry may signal quite a different need. There is another reason for long nursing. Mothers believe that while breast feeding continues, they will not become pregnant. They also believe that weaning

too early is a crime with dire consequences.

A superstition widely held is that "girl's milk" and "boy's milk" are entirely different. If a mother wishes to supplement her own baby's milk, she must find a nursing woman whose baby is of the same sex. Time and again I have heard a mother saying that the cause of a long illness was because "she was fed with boy's milk." "You see, Doctor," she would say, "I had little milk. I asked my nursing neighbor woman to give some of her milk to my little daughter. She had plenty of milk, but her baby unfortunately was a *boy!*"

Fig. 8.—The head of the baby is tightly bandaged. Pacifiers are universally used during infancy.

TRAINING

Playing with the genitals is forbidden. If a child touches his genital organ, he is slapped on the back of his hand, or shouted at, or his hand may be pricked with needles.

Pacifiers are used in infancy and even in the second and third year. The baby sucks the pacifier all the time.

Toilet training is not practiced in villages, because the babies are swaddled during most of infancy and, when they start to walk, they are actually on the spots where they are allowed to pass motion. In other words, the expression is "to go to the field." Usually there are no proper toilet facilities. That explains why the necessity of keeping clean is not considered at an early age.

Cleaning the children (as well as adults) with water, is practiced mostly near a brook, and this is why more than 90 per cent of the inhabitants of villages have different kinds of intestinal worms. Ascariasis is the commonest, then comes oxyuriasis, tapeworm, in some parts hookworm, and in a particular area called "Lar," Dragon worm.

MORBIDITY

Ringworm, *Pediculosis capitis,* and *Pediculosis corporis* are quite common among the very poor classes in towns and villages.

There are no special diets for children after they are weaned. The usual food is bread, sometimes barley bread, sour milk, cheese, and rarely meat. In a typically poor village the people eat meat only when a sheep is seriously ill and must be slaughtered or, occasionally, when an animal is killed in a hunt. In some areas dates or grapes are another cheap addition to their diets. Vegetables are not eaten, and if there are any eggs, they are sold. Because of the poor diet, hypochromic anemia and different kinds of malnutrition, particularly

kwashiorkor, nutritional edema, beriberi, pellagra, and ariboflavinosis, are common. In coastal areas tuberculosis is one of the biggest problems. Nutritional deficiencies, especially vitamin A deficiency, contribute to the seriousness of the disease. In some of the poor coastal villages, vegetables and grass are so scarce that the cows are obliged to eat small dried fish, and for this reason their milk smells of fish.

Rickets is rare, but different kinds of congenital malformations and chondrodystrophy are as common as in western nations. Small hospitals and clinics recently have been built in the small towns and large villages, but they can hardly cope with the demand.

Trachoma is the most common eye disease. In most villages more than 90 per cent of the adults are affected. It is suspected that nutritional deficiencies contribute to the etiology of trachoma in these areas, as this disease, though communicable, is not prevalent in the rich class.

It is impossible to separate the baby from the mother when the baby is ill; therefore, in our children's hospitals we admit the mother as well. This serves a double purpose: the mother feeds her baby and looks after him under the supervision of the nurse, and in addition, she learns several aspects of child care in the hospital. We use short wooden beds which remain underneath the baby's bed during the day and are drawn out at night so that the mother can sleep near her child.

SUPERSTITIONS

Medical superstition plays a tremendous part in child care in Iran. Food and drugs are divided into two groups—"hot" and "cold." Most of the carbohydrates are considered "hot." They favor the occurrence of sore throat, boils, abscesses, and different infections. "Cold," such as plum water and distilled rose water, should be administered in order to keep the balance. Certain natures are "cold," and others are "hot," and each individual should take the food or drug according to his nature. Altogether "colds" are much healthier. In instances of high temperature, the juice of watermelon and different rose waters are administered.

Purgatives are prescribed frequently. Some mothers give 10 to 20 Gm. of castor oil and almond oil together every other month to keep the baby's bowels clean. Whenever a baby has diarrhea or tenesmus, they think that the intestinal tract is not clean, or that there is an "obstacle" in the intestinal tract, and so they give purgative after purgative. This is one reason why dehydration is such a common complication, especially during the summer.

Sunken fontanel is considered a serious omen. It shows that the brain has fallen down and should be pulled up. Poultices are used for this purpose.

Rubbing the nose, shaking or banging the head, or miserable appearance in a long illness is considered to be caused by the presence of "seeds" in the upper nose near the brain. These "seeds" are drawn out by certain witches who suck the nose of the baby and deliver, no doubt from their own mouths, ten, twenty, or even fifty pieces of rice, peas, or beans. I think the number of seeds depends very much on the amount of money the poor mother can afford. The witch charges two to five cents for each seed. It

does not occur to the mother that the witch will bring all these seeds from the back of her own nasopharynx. "Doctor," the mother will say, "even though the 'seeds' have been brought out, banging of the head or fever continues all the same. Do you not think the baby has an 'obstacle' in the bowels?"

Teething is considered to be the cause of many troubles in infancy. As the course of infections in early childhood coincides, inevitably, with the eruption of one or another of the milk teeth, this interpretation has the highest credit. Fever, cough, diarrhea, vomiting, or any other symptom is attributed to teething. Second to teething as a cause of disease come worms. Febrile infections change the atmosphere and temperature of the habitat of the worm. The disturbed worm escapes either in the stool or, occasionally, through the mouth. It is not possible for the people to ignore such a big apparent "cause." They think there must be plenty more worms in the intestine which are causing the trouble. It is sometimes difficult to convince them that, for medical reasons, the administration of worm drugs should be postponed. A pediatrician in this country must be well acquainted with the significance and effects of teething and worms, which together are regarded as comprising almost all the pathology of children.

Unfortunately, agreeing with the patients and continuous family auto-suggestions have led some busy practitioners to put much store on what are but natural or insignificant events.

The "Evil Eye" is feared. Certain seeds are burned, and the soot placed on the root of the nose as a life-saving measure.

Certain doctors have a "light step." Their simple arrival at the bedside will cure the patient and change the situation for the better.

Looking for a good augury is another story. The doctor to whom to refer, the advisability of giving a drug, and other matters are decided by beads or, sometimes, books. I had a tragic case of laryngeal diphtheria where oxygen treatment was most urgent. The patient and the relatives disappeared to consult the grandmother. They promised to come back within half an hour but never returned. The next day an aunt came with a gloomy expression to get the death certificate. The "beads" had not approved of oxygen therapy! I was furious, but I could not change their minds. "The baby," she said, "would have died under the oxygen tent all the same. A more dreadful death and expensive, too."

I really should express my gratitude to the beads, because they usually approve of my medical advice. But I cannot help being occasionally annoyed when the counter of beads or seeds vetoes my therapy.

Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
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SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

THIS was the first Children's Medical Center admission of an 8-year-old boy who entered because of fever and pain in the left hip and knee.

At the age of 5 years 8 months, the patient was seen in our outpatient department because of anorexia and easy fatigability. No definite diagnosis was made at this time. The blood pressure was 130 mm. Hg systolic and 60 mm. diastolic. A soft, grade I systolic murmur, previously noted by the family physician at the age of 3 months, was heard at the base of the heart and along the left sternal border. The electrocardiogram was described as being within normal limits, with a P-R interval at the upper limit of normal. The sedimentation rate was 29 mm. per hour. No definite diagnosis was made but a diagnosis of rheumatic fever was suggested. One month later the sedimentation rate was 3 mm. per hour. Then the child was said to have had several attacks of sudden, severe pain in the lower chest and upper abdomen, associated on one occasion with dyspnea and on another with vomiting. All these symptoms disappeared and the child was not seen again until his only and final admission to the hospital.

His terminal illness began approximately three weeks before his death when he had an attack of vomiting but was well enough to go to school the next day. Two days after the onset he had a temperature of 102° F. He complained of fatigue. Three days after onset he had an epistaxis and complained of pain and tenderness in the hands, left knee, and back. His epistaxis continued daily and he developed pain in the left hip. In the week before entry to the hospital he remained anorexic and febrile, his temperature being 104° F. the day prior to admission.

The family history revealed only arthritis in the paternal grandmother and an allergic tendency in the maternal line. There was no history of rheumatic fever or heart disease.

On admission to The Children's Medical Center, the temperature was 104° F., the pulse 120 per minute, the respirations 24 per minute, and the blood pressure, arms, 120 mm. Hg systolic and 65 mm. diastolic; legs 130 mm. Hg systolic and 90 mm. diastolic. The child was thin and appeared acutely ill. He preferred to lie on his back, with his left hip flexed. Any motion produced complaints of pain.

The normal precordial impulse was felt 1 cm. outside the midclavicular line in the fifth interspace. The heart sounds were loud and snapping. There was a grade II-III, harsh systolic murmur first heard in the third left interspace; it was not transmitted to the axilla. A second systolic murmur was heard at the apex by some observers. The liver was palpable 2 to 5 cm. below the costal margin. There was pain on motion of the left hip and limitation of motion on internal rotation. A small amount of fluid was present in each knee. The peripheral pulses were all normal.

The initial laboratory data revealed the urine to be normal. The hemoglobin level was 10.5 grams per cent; the erythrocytes numbered 4.0 million and the leukocytes 14,500 per cubic millimeter, with a differential count of 74 per cent polymorphonuclears, 15 per cent lymphocytes, 7 per cent monocytes, 1 per cent eosinophils. A lumbar puncture was negative. The initial blood culture grew a *Staphylococcus aureus* in both flasks but three subsequent cultures were negative. The sedimentation rate was 63 mm. per hour and the hematocrit, 29 per cent. The Hinton reaction, a tuberculin skin test, and febrile agglutinations were all negative. The antistreptolysin titer was 500 units. An electrocardiogram revealed occasional ventricular ectopic beats and a P-R interval having a length at the upper limit of normal. A chest roentgenogram showed the heart to be enlarged to the left, with a suggestion of engorgement of the pulmonary vessels and of fluid in the left chest. A skeletal survey was negative.

The child was put on a low salt diet and given massive doses of penicillin. In three days the temperature returned to almost normal, ranging about 100° F. The pain and tenderness in the joints had subsided. The cardiac findings continued as before. On the ninth hospital day the patient again became febrile, with a temperature of 102 to 103° F. He developed pain in the left chest and was found to have left hemithorax dull to percussion, with almost absent breath sounds. The heart and mediastinum were displaced to the right. The spleen tip was palpable. A repeat chest roentgenogram showed fluid in the right pleural space and massive consolidation of the left lung. A thoracentesis produced 10 c.c. of very bloody fluid, which was sterile on culture. Oxytetracycline in large doses was used without effect on the elevated temperature. There was a gradual improvement in the chest signs and general condition. The leukocyte count remained elevated, 23,000 per cubic millimeter, and erythrocyte sedimentation rate of 40 mm. per hour.

Suddenly, on the sixteenth hospital day, the boy again complained of severe pain in the left chest and went into shock. At that time there appeared to be no change in the extensive dullness of the left chest and the marked mediastinal shift. Abdominal and rectal examinations were within normal limits. Plasma and blood were given, with improvement, but two hours later he complained of upper abdominal pain and again went into shock and did not respond to supportive measures. Prothrombin time three days before death was 35 against a normal of 17 seconds.

DISCUSSION

DR. ALEXANDER S. NADAS.*—Could we see the x-rays now, Dr. Neuhauser?

DR. E. B. D. NEUHAUSER.—The first film, Dr. Nadas, was made three days after admission. Everything appears to be quite normal, except for the heart and left chest. The heart is definitely enlarged, and although no fluoroscopic examination or spot films were made, the impression is that there is enlargement of the left ventricle. Behind the heart, at the left base, there is a vague increased density and I think there is a very small amount of fluid in the pleural space. Shortly after this, other films were made, including a skeletal survey. We could find no evidence of fluid in the knee joints. The bones appeared to be quite normal, but in the film of the abdominal region there is a definite right dorsal lumbar curve, with a left hip traction deformity. These changes suggest to us some form of irritation resulting from spasm of the hip muscles which is reflected in the spinal curvature.

The next film, five days after that, shows no change in the size or configuration of the heart, but there has been an increase in the density in the medial third of the left lung, again rather vaguely seen behind the heart. This may be either an increase in the amount of fluid in the left chest, or it is more clearly seen because of overexposure. The next film, a day later and two days before his death, shows that the left chest has increased in volume although there is still a right scoliosis. This side of the chest is wholly and homogeneously opaque. The heart and mediastinal shadows are displaced to the right and the right lung remains clear. The hip flexion and scoliosis persisted.

DR. NADAS.—Thank you, Dr. Neuhauser.

This, then, is the story of an 8-year-old boy who died after an illness of only four weeks, which today is a pretty uncommon occurrence. Eight-year-old boys usually do not die this rapidly.

In the past history, I think it is worth pointing out that a heart murmur was noticed in this boy at 3 months of age. Dr. Mary R. Richards[1] of Babies Hospital in New York published a paper about the frequency of murmurs in the newborn period. The discovery of significant murmurs in newborn babies is rare. She finds it to be about 1 per cent, and in a little older group (between 1 and 6 months), about 4 per cent. In the older age groups (1 year and beyond) one may get a 10 to 20 per cent occurrence of heart murmurs. This baby, who at 3 months of age had a definitely described heart murmur, thus had a sign to which one must pay attention.

The second significant point in the past history is that rheumatic fever was suspected in the outpatient department of this hospital. The evidence, as presented, of symptoms of anorexia, fatigue, abdominal pain, and an elevated sedimentation rate that dropped down to normal within a month, while certainly not diagnostic of rheumatic fever, is highly suggestive of it.

The present symptoms of fever, polyarthritis, epistaxis, and anorexia are suggestive of rheumatic fever. He

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has a murmur which is described as harsh, grade II-III, and is heard at the third left interspace. This is a little high and unusual in description for rheumatic heart disease. The folklore of cardiology is that rheumatic heart disease gives murmurs at the apex; congenital heart disease, around the left sternal border.

DR. CRAIG.—Would you like to hear your own description of this murmur?

DR. NADAS.—Yes.

DR. CRAIG.—The record is almost verbatim, except for the additional statement that the murmur was widely transmitted to the back.

DR. NADAS.—That is all you can read of my handwriting, I am sure.

I think we must accept the murmur as real, especially if I said it transmitted to the back. The murmur is one not commonly seen in rheumatic heart disease. Dr. Neuhauser, would you not say this is a very significant cardiac enlargement—that it is a definite enlargement, but not the configuration one associates with congestive heart failure?

DR. NEUHAUSER.—It looks like an isolated chamber hypertrophy, not the shadow of a dilated heart in failure, yet it looks significant to me.

DR. NADAS.—We have adopted, arbitrarily, the criteria that a liver more than 3 cm. below the right costal margin represents significant hepatomegaly in terms of cardiac failure. I do not know what diagnosis was made on this boy but he was started on a low salt diet. I do not know why —although I was probably responsible for it; but in retrospect, with no signs of congestive failure, it was not justified. He was also started on massive doses of penicillin, so I presume that people thought that this boy had a generalized infection. When he did not improve with this massive antibiotic treatment, the symptoms of rheumatic fever were reassessed and he was put on aspirin. I would think that at the time this child was first in the hospital (1950), aspirin would have been the first line of defense against rheumatic fever. Then, in the course of this illness which started out with joint symptoms, the dramatic event occurred which Dr. Neuhauser projected on the screen—that of a pleural effusion. Since they tapped the chest and got the blood out, if you are simple-minded about it you say that there is probably a great deal of blood in the thorax. The fact that the boy went into shock and died seems to indicate that he bled into the thorax, actively.

If you believe what you teach, this boy must have had rheumatic fever. I think you may be wrong, but you should go down with your flag fairly high on the mast because this boy has the criteria on the basis of which we teach graduate students and medical students how to make the diagnosis of rheumatic fever. This boy has objective arthritis (which is a major criterion), has an elevated sedimentation rate, fever, and an elevated streptolysin titer. These are the criteria we use in starting people on six weeks of cortisone, turning them into patients with Cushing's disease.

I think we had better stick with it and say this boy must have had rheumatic fever.

Now, the second point is equally clear—his death has not been caused by the conventional rheumatic fever

death process. This boy did not die of rheumatic carditis, you can be sure of that. In the past five years we have not lost a patient at the House of the Good Samaritan, or here at The Children's Hospital, in a first attack of rheumatic carditis. I do not know whether that is due to cortisone, whether it is due to luck, or simply intelligent general care. It would be a very unusual thing to lose a boy in three and a half weeks of acute rheumatic carditis, particularly without evidence of a pericardial friction rub, congestive failure, or arrhythmia. You have to assume that this boy did have rheumatic fever, but you cannot attribute his death to rheumatic carditis.

Third, and equally clear, there is a perfectly good explanation of why he died. He developed bleeding in the thorax. What are the causes of spontaneous hemothorax? In French's *Index of Differential Diagnosis*,[2] it is said to be erosion of blood vessels by inflammatory process. This, they say, may be due to tuberculosis or an empyema. We know he did not have tuberculosis because his old tuberculin reaction in a dilution of 1:10 was negative. He may have had empyema, but I do not know why, with no pus or bacteria in the fluid obtained on pleural tap. The rheumatic process may possibly have eroded a blood vessel somewhere in the thoracic cavity, and may have given rise to hemorrhage. I think this is the only intelligent way you could probably link these phenomena, and it is not very intelligent at that.

Dr. Diamond, what about this prothrombin time of twice normal? This was before the boy had aspirin. Is that a significant elevation?

DR. LOUIS K. DIAMOND.—I was going to ask you how long after aspirin administration one sees such a prolongation of the prothrombin time.

DR. NADAS.—Unfortunately we do not know, because we do not measure the levels, but I think the aspirin depression of prothrombin activity is very common.

DR. CRAIG.—Dr. Diamond, would not the loss of a large amount of blood suddenly increase the prothrombin time?

DR. DIAMOND.—I do not know. I rather doubt that it would produce a deficiency quite so quickly.

DR. NADAS.—You cannot attribute the bleeding to aspirin-induced prothrombin if the bleeding occurred before aspirin was given.

There is a fairly good association, based principally on autopsy findings, between rheumatic fever and congenital heart disease. Not everyone accepts it and there is a good deal of argument about it. I just want to cite the evidence that is in favor of this sort of association. Dr. Harold D. Levine (unpublished material), using autopsy data, found that as high as 14 per cent of the congenital heart disease patients who lived to be 2 years old, or older, had some evidence of rheumatic heart disease. Durlacher and Beyer[3] from Yale have also reviewed their autopsy material on congenital heart disease, and pending information on the criteria they used for the diagnosis of rheumatic heart disease at autopsy, they found a minimum of 7 per cent and a maximum of as high as 40 per cent. I do not know how good these figures are, but I think these two papers at least suggest that

there is an association between rheumatic fever and congenital heart disease.

On the basis of the murmur that was discovered in infancy, I think there is a possibility that this boy may have had congenital heart disease. Now, what kind of congenital heart disease did he have? I do not know what type of congenital heart disease he had, but there are certain things that he did *not* have. If you consider the most common congenital heart lesions in this age group which, statistically, make up from 75 to 80 per cent of the patients, you can say he probably did not have isolated severe pulmonic stenosis, because he did not have right ventricular hypertrophy. He did not have tetralogy of Fallot because he was not cyanotic. He did not have an atrial septal defect because he did not have an incomplete bundle branch block. He could have had a ventricular defect, and he could have had a coaretation of the aorta, but there is no evidence for them. If he had a coaretation of the aorta, you would expect that he would have had hypertension of the upper extremities, which he did not have, although quite a few blood pressure measurements were taken.

There is one thing I would like to say before I stop and that is—there is just one bare possibility which you could connect with the major findings, but it is so outlandish that I do not know if one should mention it. If you enumerated the types of congenital heart disease he could or could not have had, a ventricular defect and a coaretation are the two things that form a significantly large group at this age, and you cannot exclude them with certainty. I [illegible]id you could exclude coaretation on the basis of the pressures, but yet you cannot, really. If you take the blood pressure in the legs you have to be very careful about the size of the cuff you use, and if you use the same cuff on the lower extremity that you use on the upper extremity, you can get a relative hypertension in the lower extremity.[4] The only way that you can tell about this is to pay attention to the diastolic pressure in the leg, which should be identical with that found in the upper extremities, irrespective of the levels of the systolic pressure. If the diastolic pressure in the lower extremities is higher than that in the upper extremities, you have used too small a cuff on the lower extremities. Thus, you may also be getting a relatively higher systolic pressure in the legs than you would find if you used the larger cuff, or took a direct arterial tracing.

We see that this boy had a 25 mm. Hg higher diastolic pressure in the legs than in the arms, which means that his systolic pressure really may also be 25 mm. Hg higher than it was in reality. This, then, would bring his true leg pressure below that of his arm. Could this boy possibly have had a mild coaretation of the aorta which could have been the underlying lesion to which you can attach the rheumatic process, and could this, by some stretch of the imagination, have resulted in the hemothorax? Rupture of a coaretation does occur. It does not occur at this age. I do not know if we have ever seen it at this age, but it is described in older people, and Dr. Gross, in his paper on "Coaretation of the Aorta,"[5] mentions rupture of a poststenotically dilated coaretation of the aorta as causing one-fifth of the deaths with aortic rupture in

coarctation of the aorta. I do not really want to propose this too seriously because it is based on this one single piece of evidence—the height of the diastolic pressure in the lower extremities.

I would say that this boy had rheumatic fever. I would say this boy did not die of rheumatic carditis, and he had a hemothorax. He probably had congenital heart disease and thus, though statistically very improbable, I think you could possibly tie this whole thing together as a rupture of a coarctation.

DR. DIAMOND.—How about a subacute bacterial endocarditis?

DR. NADAS.—By definition it cannot be subacute bacterial endocarditis, Dr. Diamond, because he died too early. The textbooks define subacute bacterial endocarditis as occurring in people who live two months or more with endocarditis, so that this would have to be an acute bacterial endocarditis. An acute bacterial endocarditis which did not grow out cultures beyond the first two flasks, and which did not have any petechiae, just does not seem right to me, especially an acute endocarditis that would respond to aspirin by the common signs. It is just hard for me to imagine it.

DR. JANEWAY.—It seems to me that Dr. Nadas played infection awfully lightly here. This is a boy who enters the hospital with a sore hip, fever, an elevated leukocyte count and sedimentation rate. These may be classical signs of rheumatic fever, but they are also classical signs of acute inflammation of any sort. Staphylococci grew out in two flasks from the initial blood culture. They disappeared with penicillin treatment and his fever abated until he developed a hemothorax, which in itself does not cause fever. I cannot help feeling that if you are looking for an inciting agent for the rupture of the aorta, there is the possibility of some infection localizing just beyond the area of constriction, as is common.

DR. NADAS.—Dr. Massell, would you say that this boy had rheumatic fever?

DR. BENEDICT F. MASSELL.—I agree that symptoms of polyarthritis, a fever and a high antistreptolysin titer are sufficient to make that diagnosis, but what worries me is that the murmur is not that of rheumatic heart disease.

DR. CRAIG.—Do you think he had heart disease at all? According to the record, Dr. Massell, it was your impression when he was in the hospital that his murmurs were connected with physiological alterations.

DR. MASSELL.—I would like to know what his murmur was when he had no fever; it is very difficult to interpret murmurs in the presence of fever. I would agree with my statement in the hospital record—that one cannot be certain that he has rheumatic heart disease with the evidence presented.

DR. NADAS.—I agree with you. Do you accept the criteria that we have mentioned for rheumatic fever?

DR. MASSELL.—I would accept those criteria on one condition, that is, provided you cannot explain the manifestations on some other basis.

DR. CRAIG.—There was, as Dr. Nadas suggested and gave no more emphasis than it deserved from the clinical course and findings, a ruptured aneurysm just below the end of a rather long coarcted segment of aorta.

The coarcted segment extended from the innominate artery to a point below the left subelavian. The narrowed area was 1.7 cm. in length. It tapered down to a diameter of 0.5 cm. Beyond the area of the aneurysm, the aorta again expanded to 1 cm. in diameter. The aneurysm itself was approximately 2.5 cm. in diameter and the opening at the point of rupture was a little over 1 cm. in diameter (Fig. 1). The left pleural cavity contained 1,000 c.c. of fresh blood.

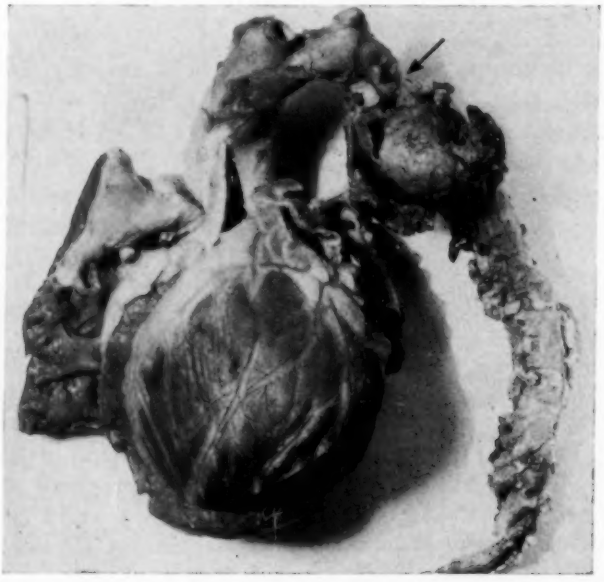

Fig. 1.—The heart and aorta. The heart is greatly enlarged. The arrow indicates the narrowest portion of the coarcted segment of the aorta just proximal to the aneurysm.

We could not find any evidence of an infection or thrombosis in the aneurysm to suggest that it had been of an infectious origin. There was no evidence of peripheral embolization in the kidney or pelvic viscera where one certainly would expect it if there had been a deposition of platelets and bacteria at the point of the aneurysm. The areas surrounding the aneurysmal sac did not suggest the presence of infection or of a rheumatic aortitis.

The problem of rheumatic fever is a difficult one here, as it is so often in children who have congenital heart disease, who have a good deal of hypertrophy. This heart was 50 per cent overweight and the left ventricular wall measured 1.7 cm. in thickness. There are areas of myocardial hypertrophy and fibrosis. However, this degree of fibrosis is frequently seen in cases of simple myocardial hypertrophy where rheumatic heart disease does not exist. We found no Aschoff bodies anywhere in the heart, and the valves, with the exception of one small thickening on one of the chordae tendineae, were not consistent with rheumatic heart disease or active rheumatic fever. The left hip was

opened, and, again, no active process was found in it.

We cannot actually say where the infection that gave rise to his early fever is located, although we do not believe it had any particular bearing on the development of the aneurysm. He had a terminal, mild pneumonia in the right lung and in the left he had only atelectasis.

This is an unusual situation, and the only one I know of in our autopsy file. As Dr. Nadas indicated, about one-fourth the people with coaretation of the aorta, in the natural course of the disease, die of a ruptured aneurysm, but four-fifths of those are proximal to the point of coaretation and not distal, the way this one was. So, this is unusual, and especially in a child of this age.

DR. MASSELL.—I would like to ask Dr. Craig a question. If the patient had a bacterial infection which was adequately treated, would the evidence for it be completely eradicated?

DR. CRAIG.—I think that is a possibility. I certainly would have expected to see (especially if there were a localization of infection at the coaretation site) some evidence of embolism in his kidney. We looked very carefully for that. The inside of the aneurysm was clean, and there were no plaques or verucae.

DR. NEUHAUSER.—I doubt that he ever had inflammation in his joints. When we first saw him he obviously had blood in the pleural space and presented a picture of psoas spasm with a referred pain to the hip region.

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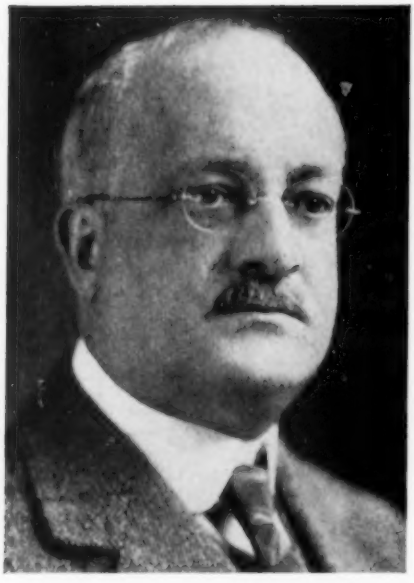
Pediatric Profiles

John Ruhräh

(1872-1935)



THIS profile is written from the fond memories of a young pediatric instructor at the Hopkins in the twenties, when the Harriet Lane staff felt so superior to all other pediatric departments, especially the one at the University of Maryland, even though ably headed by Dr. John Ruhräh. The division was so great that Dr. Ruhräh's courteous request for permission to treat one of his patients, who insisted on going to the Hopkins, was met by a firm and not so courteous refusal. Fortunately, the Harriet Lane resident, who felt badly about the situation, kept in touch with Dr. Ruhräh by telephone and carried out his orders for the care of his patient.

Also fortunately for my own relations with Dr. Ruhräh, I was greatly interested in medical, and especially pediatric, history, so he forgave me for being a lowly serf of the arrogant ivory tower across town.

It is trite to try to characterize anyone by naming his chief quality, but Ruhräh's capacity for friendship was so great that it will be remembered long after his many other virtues, and even his magnificent literary contributions. Though twenty years his junior, I felt, like everyone else who knew him, that he reciprocated my friendship for him. Arthur F. Abt and Phillip E. Rothman, even younger colleagues, fondly recall their memories of Ruhräh's kindliness. Ruhräh's contemporaries, Isaac A. Abt, Henry L. K. Shaw, Philip Van Ingen, Oscar Leser, Edgar B. Friedenwald, and, the youngest of them, Borden S. Veeder, always enjoyed Ruhräh's visits and his interesting conversation.

The younger generation, who did not have the pleasure of knowing John Ruhräh, can catch some of his

charm from the preface and introduction to his scholarly *Pediatrics of the Past,* as well as from his six other books and numerous articles on pediatric and historic subjects. There was further a "lighter side" which added to this charm. One of his friends recalls how "after an evening of music and good conversation it would end by John's reading aloud from one of his favorite books, *Gemixte Pickles.* Among these lighter sides was one that furnished much enjoyment to his many friends—his talent for light versification. This he exercised on a number of pediatric occasions, and among these his contemporaries particularly recall the lines commemorating the time the American Pediatric Society was introduced to S.M.A. by Henry J. Gerstenberger. These were sometimes privately printed for his close friends (see Infant Feeding, below). Another, also quoted below, found its way into publication in *The Journal of Pediatrics* in 1933. It reflects the period in which child psychology and child psychiatry were beginning to raise their heads, much to Joseph Brennemann's perturbation, and which led to his classic paper on the "Menace of Psychiatry," which Stanley Gibson relates in his "Profile" on Brennemann.

The following titles (and pages) of his twelve articles in volume 49 of the *American Journal of Diseases of Children* (January to June, 1935, the year in which he died) exemplify Ruhräh's versatility in writing: Adenoid Facies (1622); Carl Ludwig von Elsässer, 1808-1874; Note on History of Craniotabes (1008); Charles Michel Billard, 1800-1832; Note on History of Hypertrophy of Colon (736); Cretin or Mongol, or Both Together (477); Doctor and Poor Patient (194); Dutch Baby's Clothing (Seventeenth Century) (739); French Devices Used in Childhood (1007); Infantile Edema (1306); James Parkinson, 1755-1842; Note on History of Appendicitis in Children (474); John Abercrombie, 1780-1844; Note on History of Typhoid Fever in Children (191); Wilhelm Meyer; Note on History of Adenoids (1616); William John Little; Note on History of Spastic Diplegia (1299).

John Ruhräh holding a *borrowed* muskie (taken at the Chicago Fishing Club on Lake Court D'Oreilles, Wisconsin, in 1922, by Arthur F. Abt.)

John Ruhräh was born in Chillicothe, Ohio, September 26, 1872. The fact that his maternal grandparents were Baltimoreans may have led him to select Baltimore for his education and career. He received his M.D. from the College of Physicians and

Surgeons, Baltimore (1894). His internship and residency were at the Baltimore City (now Mercy) Hospital (1894-1897) and were followed by graduate study at the Institut Pasteur, Vienna and Berlin (1897-1900).

He became Professor of Pediatrics at the University of Maryland in 1916, and was honored by many medical and pediatric societies—president of the Medical and Chirurgical Faculty of Maryland in 1919, of the American Pediatric Society in 1925, of the Medical Library Association in 1927, of the Research Society in 1932, of the Osler Historical Society in 1933, and of the American Academy of Pediatrics in 1934. He was a member of the Board of Education of Baltimore. In 1932 he was selected by the Baltimore City Medical Society to prepare a history of the medical profession in Maryland for the last quarter of a century—a task for which he was eminently qualified.

In October, 1930, after attending the International Pediatric Congress at Stockholm, he suffered an attack of poliomyelitis, from which, after a long illness, he recovered sufficiently to enable him to resume his practice and also to travel and to engage in many of his lifelong activities, though a residual paralysis of his lower extremities persisted. He died on March 10, 1935, from a cerebral accident. He never married.

Crayon sketch of Dr. John Ruhräh.

Dr. Ruhräh made the first collective investigation of actinomycosis in the United States (1899-1900), introduced the soybean in infant dietetics (1909), wrote a useful manual of the *Diseases of Infants and Children* (1905; ed. 4, 1914); *Diet in Health*

and Disease (1905; ed. 5, 1919) with Julius Friedenwald; *Dietetics for Nurses* (1905; ed. 4, 1917); *Poliomyelitis in All Its Aspects* (1917) with Erwin E. Mayer; *Pediatrics of the Past* (1925); *Pediatric Biographies* (1932). He also contributed to Osler's *Modern Medicine,* Nelson's *Living Medicine,* Tice's *Practice of Medicine,* and Abt's *Pediatrics.* For relaxation he wrote the *History of Pediatrics, Biographies of the Old Worthies,* and *Reproduced Art of the Old Medicine.* He was active in medical library work, was instrumental in the erection of the new library building of the Medical and Chirurgical Faculty of Maryland, and was editor of the *Bulletin of the Medical Library Association* (1911).

Early in his career he came under the favorable notice of Osler, who pronounced him one of the most brilliant of the younger men and characteristically showed him the way to the heights. This inspiration was with Ruhräh to the end. It interested him in the history of medicine and the lives of its worthies; it directed him to the libraries of the world, where he was a welcome visitor; it gave him his incentive to write and made him a student of literature, whose pen was in constant demand. His last major effort was a life of Osler.

Pediatrics has been enriched by his cultured presence and illuminated by his genial, penetrating satire, sometimes phrased in clever telling verse. He entertained and instructed with the fruits of his research in pediatric history, in which he was the first authority.

Not only did he write about medical history but he collected examples of sculptures or paintings illustrating sun treatment and poliomyelitis in early Egyptian times, achondroplasia, pituitary disturbances, convulsions, and present-day child training. Of unusual interest was the record of Aztec child-training as figures in the picturographs in the Mendoza Codex. These pictures showed naming, feeding, education, and punishment at various ages from birth to 12 years. His interest in medical history persuaded Dr. Edgar B. Friedenwald to bring Cordell's *The Medical Annals of Maryland* up to date.

None could know John Ruhräh without perceiving his fine grain and the breadth and depth of his attainments. He was a man of imposing appearance—tall and erect. No one believes that his mental composure was ever disturbed. He was calm, never ruffled, keenly observant, clear in thought, and considerate in manner. His methodical habits and almost austere demeanor did not lend themselves to the usual anecdotes, but by assiduous correspondence the following have been gleaned.

A devotee of Gilbert and Sullivan, he had his own private list of those who "never would be missed." Chief of these was the bore, who suddenly confronted him and challenged, "You don't know me, I bet. Now, who am I?" His reply was always the same. "If you don't know yourself, how do you expect me to know?"

Ruhräh was very active in the Research Society at the College of Physicians and Surgeons, and at one of their meetings, Melvin Rosenthal, the dermatologist, an intimate friend of Ruhräh's and also a confirmed bachelor, said to him: "John, when are you going to marry?" Ruhräh responded, "Melvin, I am getting more

selective and less desirable, each year."

Essentially the wise practitioner, learned, experienced, and keen of insight, as well as the beloved and honored friend. His mere presence in the sickroom inspired confidence, a renewal of hope, of courage, and relief from worry, fear, or tension. Mothers, who were distracted by alarm, found in his massive figure the shadow of a great rock in a weary land. He had a matchless personality, a great faculty for forming friendships, and a gracious manner which led one to feel at home in his presence. Is it any wonder that he commanded an extraordinary personal devotion among his following? One of Ruhräh's greatest contributions to Baltimore was his initiative in the establishment of the school for disabled Negro children.

He was extremely tolerant and forgiving. He mingled with all classes of people; the lowly or untutored as well as the intelligentsia were gracefully met and with exceptional poise. However, he disliked being imposed upon. For example, while visiting the Abts on a lake in Michigan, he was summoned to see an automobile magnate with a stomach-ache. After reassuring the patient and telling him to avoid future dietary indiscretions, he was asked for his bill. Dr. Ruhräh told the magnate in plain language that the best pay for a doctor on vacation was not to disturb him.

Dr. Ruhräh was a brilliant conversationalist, frequently scintillating, always entertaining. He was often reminded of a choice tale from a rare book or a forgotten author. Combining the activities of the practitioner with a large degree of human understanding and common sense, he lived a full life. He had an artistic nature which craved cultural contacts. He read broadly, traveled extensively, enjoyed poetry, and was passionately fond of music. These intimate characteristics made it possible for him to endure, with undaunted courage and indomitable will, his severe affliction of poliomyelitis, and to resume his work and recreations, happily with some limitations. He gradually took on new tasks and carried on with joy and zest until his last illness. John Ruhräh left a rich heritage of devoted service dedicated to medicine and humanity.

Wilburt C. Davison

On reading Dr. Joseph Brennemann's "Pediatric Psychology and the Child Guidance Movement," sometimes known as Brennemann's "Dangers of Psychiatry"

THE TIMES HAVE CHANGED

In ancient days long since gone by
When Solomon was king,
The erring child who strayed from God
Was straightway brought back by a rod
It seemed the proper thing,
And sanctioned by the Holy Writ
The psyche was not hurt a bit.

One hesitates to cast a doubt
Upon the tale as voiced,
The child to elders showed respect
His conduct was most circumspect
The heavenly hosts rejoiced.
They could not pass such angels by
Which made the death rate very high.

Those days were really wondrous days
It scarcely seems 'twas true.
Whate'er the parents chanced to say
The child was taught he must obey
Or else the hour he'd rue.
The ego, in between the id
And superego, smoothly slid.

Behaviorism was unknown
In those old simple days,
No child e'er dared to answer back

For if he did he got a crack
Where now we give him praise.
The child was seen and never heard
Psychologists said not a word.

But times have changed, as proverb says,
Old things are obsolete,
We stress the feeding of the child
Which rouses ire and makes him wild,
And now he will not eat.
The more we talk, the more we fret,
The worse the youngster seems to get.

Psychologists now come to aid
With psychiatrists wise
Before the parent dares to chide
The wise guys take the child aside
And psychoanalyze.
They probe his every hope and fear
And wonder why the child is queer.

The clinic doors are opened wide
Professors sit within
The more they strive with their advice
To make the wee one mild and nice
The more the young ones sin.
They wonder what it's all about
And so do I, which lets me out.

(John Ruhräh: J. PEDIAT. 2: 391-392, March, 1933.)

INFANT FEEDING

By an Anonymous Member*

Lines Suggested by the Papers on Infant Feeding

Soranus, he of ancient Rome,
He had a simple trick
To see if milk was fit for sale,
He merely dropped it on his nail
To see if it would stick;
Yet spite of this the babies grew
As any school boy'll tell to you.

Good Metlinger in ages dark
Just called milk good or bad
No acid milk could vex his soul
He gave it good, he gave it whole
A method very sad;
Yet babies grew to man's estate
A fact quite curious to relate.

Time sped and science came along
To help the human race,
Percentages were brought to fame
By dear old Rotch, of honored name,
We miss his kindly face;
Percentages were fed to all
Yet babies grew both broad and tall.

The calorie now helped us know
The food that is required
Before the baby now could feed
We figured out his daily need
A factor much desired;
Again we see with great surprise
The babies grow in weight and size.

The vitamin helps clarify
Why infants fail to gain,
We feed the baby leafy food
Which for the guinea pig is good
A reason very plain;
And still we watch the human race
Go madly at its usual pace.

We have the baby weighed today
The nursing time is set,
At last we find we are so wise
We can begin to standardize
No baby now need fret;
In spite of this the baby grows
But why it does God only knows.

Away with all such childish stuff
Bring chemists to the fore,
The ion now is all the rage
We listen to the modern sage
With all his latest lore;
And if the baby fret or cry
We'll see just how the ions lie.

A hundred years will soon go by
Our places will be filled
By others who will theorize
And talk as long and look as wise
Until they too are stilled;
And I predict no one will know
What makes the baby gain and grow.

Should this fall into the hands of addicts of Iolanthe, it seems hardly necessary to point out that the first two treatises in this compilation can be sung to the air of "When Britain Really Ruled the Waves."—Compiler.

*Strongly suspected to be Dr. John Ruhräh.

Comments on Current Literature

ACUTE ASEPTIC MYOCARDITIS IN THE NEWBORN INFANT

MYOCARDITIS in infants,[1] described as "acute interstitial"[2] or "acute aseptic,"[3] is characterized by sudden onset "with dyspnea, paleness, cyanosis, often with coughing fits and sometimes marked tachycardia."[2] While initially the clinical picture suggests pneumonia, symptoms of cardiac decompensation soon became evident, although no characteristic cardiac murmur is heard. The electrocardiogram gives evidence of severe myocardial damage. There may be a slight elevation of temperature; however, the patient usually remains afebrile, and the sedimentation rate shows no increase. The clinical course is not a prolonged one, but progresses rapidly either to death or to recovery. On pathologic study the myocardium shows "either a granulomatous process or an inflammatory infiltrate,"[3] and while the process may be widespread, usually it is patchy.

The occurrence of acute myocarditis in infancy, particularly during the neonatal period, has been of interest for some time,[1] and the possible etiologic factors have been the subject of speculation. Within recent years the possibility of viral etiology has been discussed. As early as 1952, Gear and his associates[4] investigated a small epidemic of acute myocarditis in newborn infants in Johannesburg, South Africa. "Of ten babies affected, six died after an acute fulminating illness ending in circulatory collapse."[4] Coxsackie virus, group B, type 3, was isolated from brain tissue taken at autopsy in two fatal cases and from the feces of two infants who recovered and who were studied specifically in this respect. Simultaneously an epidemic of Bornholm disease had occurred in Johannesburg. In 1954 a similar outbreak was observed in Southern Rhodesia. Findings were reported on three infants who developed an acute feverish illness shortly after birth; one of these infants died at 12 days of age and the others recovered in about one week's time. In the fatal case, necropsy study revealed an acute focal and extensive myocarditis. Coxsackie virus, group B, type 4, was recovered from stool specimens of one of the surviving infants and from the rectum and cecum of the infant who died. A disease current in Southern Rhodesia at the time was described as similar to Bornholm disease.

Certain of these findings and others concerning the Coxsackie viruses were discussed by Dr. Gear at the Third International Poliomyelitis Conference in Rome in September, 1954.[4] Some months later Coxsackie virus, group B, was isolated from the heart muscle of a newborn infant admitted at the age of 9 days to the Transvaal Memorial Hospital for Children.[4] The child showed signs and symptoms of severe myocarditis on admission, and died soon thereafter. Autopsy studies showed a type of myocarditis similar to that described in the infants studied earlier.

In the July-August, 1956, issue of *Annales Paediatrici*[2] two papers appear (from Amsterdam and from Leyden), which throw light on this subject; likewise more recently, in the November 8, 1956, issue of the *New England Journal of Medicine*,

Kibrick and Benirschke[3] (Children's Medical Center, Boston) present a complete review of the literature, and add an interesting case of their own. In 1955 an outbreak of so-called "summer grippe" occurred in Amsterdam, chiefly in adults. During this period, four cases of myocarditis in the newborn infant were seen and studied by van Creveld and de Jager.[2] The first infant, a boy 7 days of age who was born one month before term, developed signs and symptoms of circulatory failure, including changes in the electrocardiogram. Necropsy studies revealed diffuse myocarditis with cellular infiltration and degeneration of the heart muscle fibers. In addition, there was evidence of encephalitis. The second case, that of a girl infant 8 days of age, was admitted to the hospital because of cyanosis and severe dyspnea; electrocardiographic findings indicated myocardial damage. Death occurred on the day following admission; interstitial myocarditis and meningoencephalitis were reported at autopsy. The third one of these infants, a male born prematurely, was admitted to the hospital at the age of 3 weeks with evidence of circulatory difficulty. Autopsy studies confirmed the diagnosis of myocarditis (interstitial), and revealed in addition evidence of hepatitis, encephalitis, and mild meningitis. The fourth case described by these authors was that of a full-term infant, who suddenly showed signs of illness on the seventh day of life, and died about one hour later. Necropsy findings were not remarkable except for a diffuse myocarditis.

The authors emphasize the fact that all four of these cases of fatal interstitial myocarditis in infants occurred within a two-month period when "summer grippe" was prevalent in Amsterdam. From a clinical point of view it seemed significant that in the case of the first infant, the mother had suffered from an influenza-like illness with high fever, onset occurring two days before delivery. In the case of the second infant, the mother experienced three short febrile episodes beginning about three days post partum. The father likewise experienced an influenza-like illness. Several children in the neighborhood were known to have had "summer grippe." In the case of the fourth infant, whose illness was fulminating and of short duration, the mother was attended by her physician on the fourth and fifth days post partum because of a febrile illness (39° C.) similar to that occurring in neighborhood children at this time.

Following the article by van Creveld and de Jager is a report in the same issue by their colleagues, Verlinde, van Tongeren, and Kret,[2] who carried out biological investigations on the four patients described, and who include also the results obtained in a fifth case which was studied by Dekking of the Laboratory for Hygiene, University of Amsterdam. By means of HeLa cell tissue cultures and the inoculation of one-day-old suckling mice, strains of virus were isolated from the heart muscle of all five infants and from the brain of one. Appropriate neutralization tests identified the strains as belonging to Coxsackie group B, type 4. Neutralization tests were possible also on blood specimens obtained from a limited number of patients in the community who had suffered during this summer period from pleurodynia, aseptic meningitis, or influenza-like illness. In the case of three of these, two with pleurodynia and one with aseptic meningitis, Coxsackie virus, group B, was isolated from fecal specimens. Cross-neutralization studies suggested that the strains of virus isolated from the newborn infants were in all probability the same as those causing illness among older members of the population.

A study carried out in cynomolgus monkeys is of special interest. It has been the general observation that

older monkeys show only mild or subclinical evidence of infection following inoculation with strains of Coxsackie virus, at the same time carrying the virus and acquiring antibodies. An attempt was made to infect cynomolgus monkeys with the newly isolated "myocardial strains" of Coxsackie virus. When monkeys approximately 6 months of age were inoculated intracerebrally with these strains, a febrile reaction (temperature 39.8° to 40° C.) occurred about the third day following inoculation. Virus was recovered readily from the blood of these monkeys. No clinical signs of illness were apparent. However, a newborn cynomolgus monkey inoculated intramuscularly with the "myocardial strain" on the second day of life became fatally ill, with onset about forty-eight hours after inoculation, the chief manifestation in addition to fever being severe dyspnea. Autopsy studies revealed degenerative changes in the heart muscle, a local degenerative myositis at the site of inoculation, and evidence of meningeal irritation. Virus was recovered from the heart muscle and from the brain of this newborn monkey. From these detailed studies of Coxsackie infections occurring in the Netherlands during the summer and early autumn of 1955, the Dutch investigators concluded that the strains of virus recovered from the heart muscle and brain of infants who died with histologically proved myocarditis were identical with each other, and with the three fecal strains isolated during the same period from older patients with pleurodynia and aseptic meningitis.

In the review and case presentation by Kibrick and Benirschke[3] the authors describe clinical and pathologic findings which support the conclusion that Coxsackie virus, group B, type 3, was responsible for myocarditis and meningoencephalitis in a newborn infant and contribute the important information that this infection must have occurred transplacentally during intrauterine life. The complete case report is included with an account of the pathologic findings and the laboratory studies for virus isolation. The mother of this infant was well until the thirty-eighth week of pregnancy when she developed "an upper respiratory infection characterized by coryza, sneezing, and malaise." Two days later a cesarean section was performed because of the diagnosis of placenta previa. The infant, who weighed 8 pounds 4 ounces at birth, developed a croupy cough with inspiratory crow within a few hours. She did fairly well, however, until the third day of life when the temperature which had been 97° to 98° F. suddenly rose to 100.2° F.; the infant became lethargic and took feedings poorly. Physiologic jaundice and pedal cyanosis were present. Lumbar puncture revealed xanthochromic spinal fluid with 132 cells, 95 per cent of which were mononuclear cells. Fever (101.4° F.) and lethargy continued; a second lumbar puncture yielded xanthochromic fluid containing 98 red cells and 132 white cells per cubic millimeter, 90 per cent of which were mononuclear. The infant's condition worsened appreciably on the sixth day of life, and death occurred on the seventh day. Complete autopsy examination revealed a diffuse myocarditis, scattered areas of encephalitis, and degenerative and inflammatory lesions in the anterior horns and in the reticular formations of the spinal cord. A portion of the thoracic cord was available for biologic study; from this material Coxsackie virus, group B, type 3, was isolated by means of tissue culture, chiefly human embryonic skin and muscle preparations. A blood specimen from the mother, taken twenty-one days post partum, showed the presence of neutralizing antibodies to the Coxsackie virus.

The findings in this excellent study support the authors' conclusion that this infection in a newborn infant must have been acquired during intrauterine life, and that in all probability the viral agent crossed the

placental barrier, establishing the infection during the prenatal period. As the authors point out, "the nomenclature for this condition is complex and confusing"[3]; "acute myocarditis," "acute interstitial myocarditis," "idiopathic myocarditis," and Fiedler's myocarditis have been noted in the literature. Consequently the suggestion is made by these authors that "such cases be given the nosologic designation 'acute aseptic myocarditis,'"[3] since the situation appears similar to that obtaining in certain meningitides which was simplified by the general adoption of the designation, "acute aseptic meningitis."

From the observations and results reported in these articles it seems clear that strains of Coxsackie virus constitute the etiologic agent producing this striking picture of myocarditis in newborn infants, and that although other tissues such as those of the brain and the liver may be involved, the most prominent pathologic changes center in the myocardium. The importance of influenza-like illness occurring in the mothers during the latter part of pregnancy and of the concurrent outbreaks of Coxsackie infection in the community is well brought out by these studies.

RUSSELL J. BLATTNER

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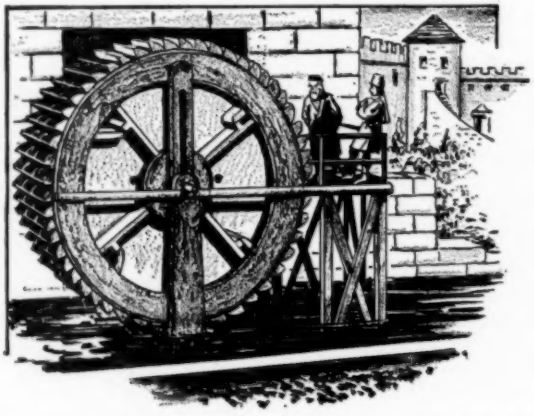
Correspondence

To the Editor: A Note on Air-Conditioning in Infancy

It was thought that Duke was the first hospital to install air-conditioning for patients except premature infants.[1] It was done in 1929, not with the idea of increasing their comfort as is the rule today, but because of the excellent work of Dr. Katherine Dodd at Vanderbilt in demonstrating that cooling diarrheal infants decreased their fever.[2] She did it by placing the infants in cribs next to a tub containing a block of ice and having an electric fan blow the chilled air over them. As a result of that work, six children's rooms in Duke Hospital were equipped with the most modern (at that time) electric air-cooling.

Now we know that the advantage of the coolness was that it reduced dehydration, a condition which at present can be controlled by injecting additional fluids into the infant. We have also learned how to reduce the incidence of infant diarrhea by feeding all the children lactic acid milk, and administering sulfonamides to any children who were not being fed lactic acid milk and who developed diarrhea. Therefore the infants do not need air-conditioning, and the adult patients, particularly the asthmatics, are using it. More recently, many of the patients' rooms have been air conditioned primarily for their comfort, although hospitals also need air-conditioning to prevent heatstroke in patients operated upon and those who have had endoscopic examinations, atropine, and reduced food and fluid intake.[3]



From *Time*, Sept. 10, 1956, p. 123; permission requested from *Time* and Borg-Warner.

Hospital cooling, however, antedated modern electric devices. It was learned from Major General S. B. Hayes, Surgeon General, United States Army,[4] that in 1876 the United States Soldiers' Home Hospital in Washington was equipped with air-conditioning. Undoubtedly that is the first instance of air-conditioning for the comfort of patients. A mechanical blower in an adjacent building, connected to a steam engine, blew air over a supply of water

and forced this cool air throughout the Soldiers' Home Hospital. In the winter, the same fan blew air over steam pipes. Apparently the results were not satisfactory because sometime before the end of the century this cooling, heating, and ventilating apparatus was removed and steam heat installed.

It also is interesting that a South Carolina physician, who later moved to Florida, Dr. John Gorrie, invented mechanical refrigeration in 1851, which forms the basis for all modern air-conditioning.[5] Dr. Gorrie did his work in order to make ice to cool a febrile malaria patient.

Air-conditioning for comfort alone has an even longer history. In the sixteenth century, Leonardo da Vinci designed a huge water wheel (Fig. 1) which forced water-cooled air into the boudoir of the Duchess D'Este.

WILBURT C. DAVISON

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In last month's (April) issue a letter received from Dr. H. R. E. Wallis of Bath, England, was published, strenuously objecting to a review criticizing his recent monograph on *Masked Epilepsy* in our December issue. We were quite agreeable to publishing his dissent, although no answer was made as it could only lead to controversy based on differences of opinion.

After our April issue was in press, the December, 1956, issue of the British pediatric journal, *Archives of Disease in Childhood*, was received. It contained a review of Dr. Wallis' monograph from which we quote a few remarks, as the review quite independently confirms the judgment and validity of the criticisms of the JOURNAL reviewer:

". . . and to claim that this discovery is a new one, removes the monograph from the realms of serious scientific communication.

"The author says, for instance, that 'it is generally admitted that if a disorder responds to anti-convulsant drugs it may legitimately be called epileptic . . . and that any obscure periodic disorder which responds to treatment with it [phenobarbitone] is probably epileptic.'

"At 7s. this monograph is expensive, tendentious and misleading."

News and Notes

The following were certified by the **American Board of Pediatrics** at the examination at New Orleans, La., Feb. 22, 23, 24, 1957.

Dr. Ata Bakshandeh, 41-42 Elbertson St., Elmhurst, L. I., N. Y.

Dr. Irvin B. Braverman, 1132 W. Lunt, Chicago 26, Ill.

Dr. James William Caldwell, 606 S. Broadway, McAllen, Texas.

Dr. Victor C. Calma, University of Texas Medical Branch, Department of Physiology, Galveston, Texas.

Dr. Enrico Dederick Carrasco, U. S. Army Hospital, Fort Knox, Ky.

Dr. Robert L. Clark, 1301 Flushing Rd., Flint, Mich.

Dr. Bernard Cullen, 1404 Kings Rd., Leesville, La.

Dr. Joseph McDonald Damron, 202 N. Washington St., Winchester, Va.

Dr. Sarah Fredericka Davis, 2251 Highland Ave., Birmingham 5, Ala.

Dr. Edwin B. Dempsey, 809 N.W. 12th St., Andrews, Texas.

Dr. Edward Earl Donaldson, 881 Enfield Rd., Columbus, Ohio

Dr. Fred Iverson Dorman, Jr., 2010 New Jersey Rd., Lakeland, Fla.

Dr. Frances Ingell Doyle, Pyatt Memorial Medical Building, 1109 Memorial Lane, Georgetown, S. C.

Dr. Andrew Cornell Erlanson, 2177 Randolph Ave., St. Paul, Minn.

Dr. Donald Joseph Frank, 2546 Auburn Ave., Cincinnati 19, Ohio.

Dr. Richard A. Frankel, 6303 S. Park Blvd., Houston, Texas.

Dr. Marshall Bernard Greenman, 8716 Warner, Richmond Heights, Mo.

Dr. Irving Edward Hall, Jr., 1224 Manatee Ave., West, Bradenton, Fla.

Dr. Leonard Harris, 800 Grand Concourse, New York 51, N. Y.

Dr. Hector Osvaldo Hidalgo, Box 8384, Juncos Station, Santurce, P. R.

Dr. James Kirtley Hill, 1095 Third St., Muskegon, Mich.

Dr. William K. Howard, 607 Medical Arts Bldg., 1211 Twenty-First Ave. South, Nashville, Tenn.

Dr. Ann Hunt, University of Arkansas Medical Center, Little Rock, Ark.

Dr. Marshall H. Klaus, 1316 Grant Ave., Novato, Calif.

Dr. Wilbur Glenn Lawson, Newman Clinic, Shattuck, Okla.

Dr. James Willard Lewis, Marshall Field Clinic, 1800 Wilson Ave., Chicago 40, Ill.

Dr. George Richard Logsdon, 125 DeSoto St., Pittsburgh 13, Pa.

Dr. Evelyn June Lorenzen, 3911 Montrose Blvd., Houston, Texas.

Dr. Bailey J. Lovin, Jr., 5830 Overhill Dr., Los Angeles, Calif.

Dr. James Robert McCain, 1400 Avondale Ave., Jacksonville, Fla.

Dr. Robert Seidel McCurdy, 462 Hawthorne, Boulder, Colo.

Dr. Duncan Hugh MacNamee, 903 Mason Blvd., Marion, Ind.

Dr. William C. Mannschreck, 628 Fifth Ave., Lewiston, Idaho.

Dr. Gerard Marder, Akers Center, Gastonia, N. C.

Dr. Brown Crosby Mason, 3439 Prytania St., New Orleans 15, La.

Dr. Sanford John Matthews, 1293 Peachtree St., Atlanta, Ga.

Dr. John Clifton Moore, Jr., 2012 Seminole Trail, Lakeland, Fla.

Dr. William Melville Mulholland, 1801 Lyndale Ave. South, Minneapolis, Minn.

Dr. William Allen Newton, Jr., The Children's Hospital, Columbus 5, Ohio.

Dr. William W. Nicholls, 1301 Flushing Rd., Flint 4, Mich.

Dr. Rosalind Novick, 1522 2nd St., New Orleans 13, La.

Dr. Ralph E. Nyhus, Mayo Foundation, Rochester, Minn.

Dr. Bernard Anthony O'Hora, 110 West Sugnet Rd., Midland, Mich.
Dr. Roland Wingate Penick, 100 S. Memminger St., Greenville, S. C.
Dr. Clifton Robert Peterson, 2nd General Hospital, APO 180, New York, N. Y.
Dr. Doris Sturgis Phillips, 4212 Avenue V, Birmingham, Ala.
Dr. Virginia E. Pomeranz, 36 Sutton Pl. South, New York 22, N. Y.
Dr. Morris A. Price, 1645 San Marco Blvd., Jacksonville, Fla.
Dr. James Joseph Reilly, 117 Hibiscus Dr., Pittsburgh, Pa.
Dr. Adelaide E. Sauers, 3090 E. Livingston Ave., Columbus, Ohio.
Dr. Mervin Herbert Schwartz, 5017 Knox Dr., El Paso, Texas.
Dr. John Franklin Shriner, 1916 Grant St., Mobile, Ala.
Dr. Robert M. Siegel, 110 Walnut Hill Village, Dallas 20, Texas.
Dr. Homer D. Venters, Jr., 546 McCallie Ave., Chattanooga, Tenn.
Dr. John Vernon Wilber, 1622 E. Market, Warren, Ohio.
Dr. Walter Llewellyn Wilder, 6424 Ryan Ave., Minneapolis, Minn.
Dr. Thomas M. Wiley, Jr., 2205 McGregor Blvd., Fort Myers, Fla.
Dr. John B. Young, 3837 Bellaire Blvd., Houston, Texas.
Dr. Martha Dukes Yow, 1200 M. D. Anderson Blvd., Houston, Texas.

Dr. Myron E. Wegman has been appointed Secretary General of the Pan American Sanitary Bureau, Regional Office of the World Health Organization. In the position of Secretary General, Dr. Wegman will be the Bureau's chief planning officer, responsible for coordinating the program planning of the Organization in the light of the health needs of the member countries. Since 1952 Dr. Wegman has been Chief of the Bureau's Division of Education and Training, working with medical schools, public health schools, and other educational institutions, which has brought him into close association with all the governments and public health administrations in the Americas.

A *Fellowship in Newborn Research* is available in the Department of Pediatrics of the **University of Pittsburgh School of Medicine,** beginning July 1, 1957. A balanced program of research, clinical training, and teaching is offered. Completion of two years of approved pediatric residency is required for eligibility. The stipend is $4,000 per year. For further information, write: Dr. E. R. McCluskey, 125 DeSoto St., Pittsburgh 13, Pa.

The Board of Trustees of **The American Foundation for Allergic Diseases** announces the availability of three *Fellowships in Research and Clinical Allergy* for a period of two years each, carrying a stipend of $4,500 for the first year, $4,750 for the second, and a total of $750 for laboratory and travel expenses during the two-year period. The Foundation has established single fellowships with three investigators eminently qualified to teach the principles and techniques of scientific method in this field and in institutions where adequate clinical facilities exist. Applicants should apply directly to one of the following investigators who will make the final selection: Dr. Frederick G. Germuth, Jr., The Johns Hopkins University Medical School, Baltimore 5, Md.; Dr. Colin M. MacLeod, University of Pennsylvania, 820 Maloney Clinic, 36th and Spruce Sts., Philadelphia 4, Pa.; or Dr. Herman N. Eisen, Washington University School of Medicine, St. Louis, Mo.

Candidates must be graduates of approved medical schools and must have completed the graduate training required as a preliminary to certification by the Boards of Internal Medicine or Pediatrics; they are to divide their time between research and clinical training, and in the second year 10 or 15 per cent of a candidate's time might be devoted to teaching.

Applications should be received by May 10, 1957.

A *Fellowship in Pediatric Cardiology* is being offered at the John Gaston Hospital and the Division of Pediatrics of the **University of Tennessee,** Memphis. The position is available for a period of one year starting July 1, 1957, and carries a stipend of $3,600 per annum. Candidates should

have a minimum of a one-year pediatric residency or its equivalent. Requests for application may be made by writing to Dr. F. Tom Mitchell, University of Tennessee, College of Medicine, Memphis, Tenn.

Applications for the residency from Jan. 1, 1958, to Dec. 31, 1958, in *Pediatric Oncology* at **Memorial Center for Cancer and Allied Diseases** in New York will be received up to Aug. 1, 1957. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary: $3,600 annually plus maintenance. For application forms and information write: Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 East 68th St., New York 21, N. Y.

An unrestricted grant of $10,000 has been made to the Department of Pediatrics of the University of Louisville by the *Courier-Journal* and *Louisville Times Foundation*. The grant is to be used by Dr. Frank Falkner in a study of identical twins as part of the work of the Department's Child Development Unit.

The **Seventh Annual Research Equipment Exhibit and Symposium** will be held May 13 to 16 at the National Institutes of Health, Bethesda, Md. There will be approximately 100 displays of the latest research instrumentation. At the symposia the topics for discussion will include Biological Data on Processing and Computation, Automation in the Laboratory, Mass Spectroscopy, and Tissue Cultures.

Books

The British Paediatric Association—1928-1952. H. C. Cameron, London, 1955, The British Paediatric Association, 107 pages. Price 12s.6d.

Pediatricians will find much of interest in this history of the British Paediatric Association. Dr. Hector C. Cameron, the author, has selected his material in a remarkable way, which presents not only the story of the Association, but also an account of the many changes and developments in British pediatrics that took place during the twenty-five years covered. The Association was organized in 1928, largely through the efforts of Donald Paterson and the late Sir James Spence. Interestingly, this was the same year the American Pediatric Society was celebrating its fortieth anniversary and during these forty years American pediatrics had been greatly influenced by the early British pediatricians.

For the first eleven years the meetings, usually at Lake Windermere, are described as sort of a "friendly club." A three-hour morning session ". . .when communications were made; the afternoon was left free for golf, fishing, or motor trips; in the evening the annual dinner when the toasts of the Association and of the President were proposed and duly honored." Another three-hour session the following morning and the meeting was over. The account vividly recalls the meetings of the American Pediatric Society from around 1912 to 1930, when there was much the same atmosphere of friendliness and intimacy.

With World War II came an abrupt change in the character of the organization. The chapter "The War Years" is to the non-British pediatrician the most interesting. Under the leadership of Parsons and Spence the Association found itself involved with many important problems. One marvels at what was accomplished during these distressing times. Committee studies and reports on such subjects as neonatal mortality, breast feeding, juvenile delinquency (child guidance), milk, immunization, and vitamin D. Further it was during this period that largely through the efforts of the Association pediatrics was given "due place" in the medical schools and final examinations. It was toward the end of these years that "Comprehensive Medical Service" was under

discussion, which terminated in the National Health Service Act of 1946. This involved the position and pay of consultants, the control of hospitals, and many other subjects of importance to the pediatricians in view of the radical changes being brought about in medical practice. It is only when one reads the Report of the Activities of the Executive Committee from December, 1943, to July, 1945, which ends the chapter, that the change in the Association from a "friendly club" to an important constructive organization is fully realized. It adds to the respect we have always held for British pediatrics.

"When in 1945, victory was won, paediatricians, like everyone else, found themselves in a changed world." With this sentence Dr. Cameron takes up the post-war years 1945 to 1952. Nevertheless, the Association, which had so rapidly reached maturity during the war years, went back to the annual meetings at Lake Windermere. There was so much to be discussed that the length of the meeting was increased to two and one-half days, thus happily without the necessity of omitting the "holiday" spirit and friendliness of the meetings.

The author not only has exercised judgment in his selection of material, but also has a facile pen which makes the history delightful reading. There are many brief pen pictures of the members, as well as sketches of the deceased members, at the end which make the history alive and not simply a text of factual and statistical information as is so often the case in books of a similar character.

B. S. V.

Handbook on Poliomyelitis. Joseph Trueta, M.D., F.R.C.S., A. B. Kinnier Wilson, M.R.C.P., and Margaret Agerholm, B.M., B.Ch., Springfield, Ill., 1956, Charles C Thomas, 139 pages. Price $3.75.

A handbook on poliomyelitis published simultaneously in England by Blackwell and in Canada by The Ryerson Press. The senior author is professor of orthopedics at Oxford, Dr. Wilson is an orthopedist on the staff of the Poliomyelitis Centre of the Royal National Orthopaedic Hospital, and Dr. Agerholm is a member of the staff of the Nuffield Orthopaedic Centre at Oxford. After brief introductory chapters on the virus, the precipitating factors in the individual, pathology, and diagnosis, the larger part of the text is a discussion of treatment and management of the various stages of the disease. The volume is of interest to those engaged in the care of patients with poliomyelitis rather than to physicians in general.

Pica. Marcia Cooper, Sc.D., Springfield, Ill., 1957, Charles C Thomas, 114 pages, Price $3.75.

The first half of the monograph is an interesting historical review of pica, going back a number of centuries. The second part presents the author's study of the incidence of pica among children referred to the Mothers Advisory Service of the Division of Mental Hygiene of the Johns Hopkins School of Hygiene. In all, there was an incidence of pica in the histories of 22 per cent of 784 children in the study. The study confirms the increased frequency of pica in the Negro race. Intelligence did not seem to be a factor. The pica group showed an increase in illness and physical defects over the control group, but no statement is made as to whether this is regarded as cause or effect. There was an increase of "feeding problems" in the pica group. The author suggests that poor nutrition may be the underlying factor, but offers no real evidence to support the hypothesis. While the historical discussion is very well done and interesting, the author's study throws no light on the subject.

Advances in Pediatrics, vol. IX, 1957. Edited by S. Z. Levine, M.D., Chicago, 1957, The Year Book Publishers, Inc., 336 pages. Price $9.00.

The 1957 edition of *Advances* contains six excellent and timely reviews written by men well qualified to discuss the particular subject: Postmaturity by Stewart H. Clifford; the Gamma Globulins by Janeway and Gitlin; Thyroid Disorders in Childhood by Wm. A. Reilly; Familial Dysautonomia by Conrad Riley; Fluoridation by E. B. Schlesinger and D. B. Ast; Coagulation Disorders in Infancy and Childhood by Irving Schulman and Carl H. Smith; Celiac Disease by

Weijers, Van De Kamer and Dicke of Holland. All of the reviews are followed by extensive references, and the volume itself has a good subject index.

The Nature of Brucellosis. Wesley W. Spink, M.D., Minneapolis, 1956, University of Minnesota Press, 464 pages. Price $8.00.

An interesting monograph based on the investigations which have been carried out at the University of Minnesota the last twenty years. The first chapter on the evolution of the concept that brucellosis is a disease of animals and man is a very interesting essay of historical interest. From then on the text discusses the brucella cells, the epidemiology of the disease, and brucellosis from the standpoint of its course, complications, and therapy. An extensive Appendix contains the protocols of 139 cases proved bacteriologically and of 145 cases not proved bacteriologically. Finally, a valuable bibliography of over 900 references.

Angiocardiographic Interpretation in Congenital Heart Disease. H. L. Abrams and H. S. Kaplan, Springfield, Ill., 1956, Charles C Thomas, 240 pages. Price $11.75.

This book is divided into two sections. Section I takes in the following subjects: (A) Angiocardiographic Technique and Equipment; (B) Reactions to Opaque Media and Angiocardiography; (C) Angiocardiographic Interpretation; (D) Technique of Aortography. Section II discusses specific congenital cardiac abnormalities. The chief value of this book is found in the excellent reproductions of roentgenograms of angiocardiograms supplemented by diagrammatic anatomic sketches.

Oto-Rhino-Laryngologie Infantile. A. Lemariey, with the collaboration of H. Muler, Paris, 1956, Masson et Cie, 826 pages. Price 6,200 Fr. francs.

Dr. Lemariey, oto-rhino-laryngologist to the Hôpitaux de Paris, has written a most exhaustive text of 826 pages which is of more interest to the nose and throat specialist than to the pediatrician, as it considers many technical details of operative procedures. Its very completeness, however, makes it an excellent book of reference.

Chirurgie orthopédique des paralysies. R. Merle d'Aubigné, J. Bénassy, and J.-O. Ramadier, Paris, 1956, Masson et Cie, 431 pages. Price 5,000 Fr. francs.

A technical manual of interest to the surgeon rather than to the practitioner. The various chapters detail the management and surgical treatment of various types of paralysis. One chapter discusses spastic paralysis in the infant, and there is an excellent chapter on the re-education of patients with paralytic poliomyelitis.

Practical Dermatology. S. M. Peck, M.D., and L. L. Palitz, M.D., New York, 1957, McGraw-Hill Book Co., 380 pages. Price $7.00.

A text intended for the general practitioner by dermatologists on the staff of the Mt. Sinai Hospital in New York. It is largely concerned with treatment based on the personal experience of the authors. It is essentially a practical manual rather than a text on dermatology. The writing is clear and direct. There are numerous illustrations.

Current Therapy 1957. Edited by Howard F. Conn, M.D., Philadelphia, 1957, W. B. Saunders Co., 731 pages. Price $11.00.

The annual volume on current therapy to which over 200 physicians have contributed. It follows the same format and plan of previous editions.

Foundations of Nutrition. ed. 5. Clara Mae Taylor and Grace Macleod, New York, 1956, The Macmillan Co., 620 pages. Price $5.90.

Considerably revised, with new tables.

Synopsis of Pathology, ed. 4. W. A. D. Anderson, M.D., St. Louis, 1957, The C. V. Mosby Co., 829 pages. Price $8.75.

A revised edition, bringing in the advances since the third edition in 1952.

Bone Structure and Metabolism. Proceedings of a Ciba Foundation Symposium, Boston, 1956, Little Brown & Co., 299 pages. Price $8.00.

The papers and discussions of a symposium held in 1955.

Editor's Column

ARE THERE TOO MANY PEOPLE IN THE WORLD?

IT IS rather a jolt to our complacency and to the satisfaction we have enjoyed of belonging to a profession that has contributed so much to the health and happiness of mankind, to find there is a group of ecologists who feel medical progress has been an important factor in bringing about the troubled world that exists today. At least that is the implication of their studies and reports, and pediatries is a chief offender.

The contention is a reiteration of the Malthusian doctrine that our troubles are due to overpopulation resulting from the rapid increase in world population, stated to be 100,000 a day. The world population is estimated by United Nations statisticians as:

1,810 million in 1920
2,250 million in 1940
2,504 million in 1950
2,652 million in 1954

Thus in the last twenty-five years the world population has increased roughly 50 per cent.

This increase of 2 per cent a year has been brought about by an excess of births over deaths. In Ceylon, for example, the birth rate has remained at 40, while the death rate has declined from 20 to 10. Even in Japan, where the birth rate is stated to have been kept at 19.4 per 1,000 by an estimated million and a half abortions a year, the population has increased to 90 million and is said to be reaching an "explosion point." The problem of overpopulation is not limited to the Asiatic countries as India, nor African as Egypt, but is developing in some of the American countries. It is estimated that at the current rate of increase the population of Mexico will double in twenty-five years, a jump from 30 to 60 million. Puerto Rico, our direct responsibility, is sorely troubled with population problems.

The decrease in the death rate, which has occurred in so many countries, is considered as resulting from the advances made in medicine and sanitation. Western-developed pediatric knowledge and practices, which in the last fifty years have reduced the infant mortality rate from well over 100 to less than 30, are being rapidly introduced throughout the world, and are responsible for a considerable part of the decrease in death rates. The death rate moreover has been lowered in many countries with little change or progress in the traditional ways of living for the masses of the population.

Population growth is far outstripping food production. It is stated that half of the people in the world today are hungry. Hunger breeds discontent and trouble. The world-wide increase in food production is calculated as 1 per cent a year, while

the population increase is 1.5 per cent. Further, the food increase is not uniform in distribution with the population increase. In the Far East, not including China, the gain in food is only 0.04 per cent a year compared with a population growth of 1.3 per cent. Although it has been shown in this and other Western countries that improved chemical and mechanical methods of agriculture can produce more food from less land, sufficient production to meet the needs of the people is lagging far behind in countries less favorably situated from the standpoint of natural resources and economic development. Paradoxically, despite a rapidly increasing population, food problems in the United States are centered at present on the political and economic aspects of a surplus of food.

In the United States, which has one of the highest rates of increase in the world, 2 per cent a year, population problems have developed of a different nature, which are minor compared with those of many of the Eastern and Mid-eastern countries. Not so many years ago when the word "dependent" was used, it almost automatically referred to a child. Today our sociologic thinking in this country is far more concerned with the economic and social problems of a rapidly increasing "old age" group. In fact, it is this group that has led to revolutionary changes in our social and economic structure within the last twenty years.

It is no wonder that the hungry people in the overpopulated, underdeveloped countries in the world are stirred up and discontented, particularly since modern methods of communication have brought to the masses of population knowledge of the high standards of living enjoyed by most of the people in the Western world. In their understandable dissatisfaction resulting from poverty and hunger, it is only natural that they fall easy prey to the blandishments of political leaders who offer political and social schemes promising improvement in their standards of living and way of life.

Throughout the ages war and pestilence have been the great population levelers. The threat of pestilence has been eliminated to a great extent by the medical scientist. It is rather ironical that due to the advances in knowledge made by another group of scientists the world is in danger of returning to an era comparable to the "Dark Ages." Certainly if global warfare were to occur today, overpopulation would no longer be a problem.

So far the only suggestion we have seen offered to check the steady and rapid increase in world population has been "birth control." To our way of thinking this is a mere "wish thought." There is nothing practical about it for such overpopulated countries as Egypt, where illiteracy is said to be 85 per cent, and India with 90 per cent. Added to this are other factors, such as customs and tradition, and religious beliefs.

Overpopulation in many countries is an existing fact. Whether it is the chief cause of the turmoil in which the world finds itself today may be debatable. Common sense, however, tells us that it unquestionably is an important factor. Just how much of a role medical progress has played is an interesting question to ponder over, particularly to the pediatrician.